Nanocrystals A Recent Advancements in Medicine

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I. INTRODUCTION:

A major challenge in creating new medicines today is that many new drugs don't dissolve easily in water. If a drug doesn't dissolve well, our bodies have a hard time absorbing and actually using it. To fix this problem and help the drug dissolve better, scientists generally use two main approaches: changing the drug physically or changing it chemically. Making physical changes involves altering the drug's physical state without changing its core chemical makeup. Scientists might do this by shrinking the particles down into microscopic or nano-sized pieces, altering the physical crystal structure of the drug, or mixing it with helpers—like specific carriers, solvents, or compounds like cyclodextrins—that help pull it into the liquid. On the other hand, chemical changes involve slightly tweaking the drug's chemistry to make it more water-friendly, such as turning the drug into a salt or creating a "prodrug". Out of these methods, making the drug particles smaller has been a clever, reliable go-to approach for many years. When you break a drug down into tiny pieces, it exposes much more of the drug's surface area to the liquid. Because more of the drug is touching the liquid, it dissolves and gets absorbed into the body much faster. However, it is worth noting that for drugs that are extremely stubborn and barely dissolve at all, just making the particles smaller might not be enough. (1)

The process produces micro particles together with nanoparticles when drugs or carriers undergo size reduction. The small dimensions of these nanoparticles provide them with numerous surfaces enabling increased dissolution rates. The drug substance exists within the formulation matrix as well as distributing on the outer surface of the particles. The pharmaceutical industry uses various nanoscales devices which include micelles liposomes solid lipid nanoparticles polymeric nanoparticles PEGylated nanostructures nanocrystals cyclodextrin dendrimers nanotubes and metallic nanoparticles. Scientists can direct nano- particle adsorption to certain tissues or organs through changes in surface polarity and surface attributes together with modification of particle charge. The research demonstrated that these nanoparticles function as effective delivery systems for gastrointestinal tract and blood-brain barrier mucoadhesive applications. (2)

The scientific community has conducted extensive research on nanocrystal drug technology, which now presents opportunities for additional investigation in drug delivery research. The nanocrystal formulation method has successfully recovered multiple hydrophobic drugs. The approved formulations for each disease can be administered through various routes which include oral and dermal and parental delivery methods. The nanocrystal drug platform demonstrates its capability to create multiple drug delivery systems. The researchers evaluated pharmacokinetics biodistribution and bioavailability data for organs that participated in nanocrystal technology delivery tests. The scientific community has published multiple articles which describe how researchers create nanocrystal drugs and the specific stabilizers or surfactants they use and the techniques they employ to conduct physicochemical and biological tests. The highly promising platform shows a wide translational gap which prevents its use in clinical settings. In this review, we discuss the nanocrystals drug technology and its development from a translational perceptive. (3)

The therapeutic applications of products containing nanocrystals extend to targeted drug delivery and all available administration methods which include oral and parenteral and ophthalmic and cutaneous and pulmonary routes. There are multiple ways to give nanocrystals, unlike micronised medications. The preferred method of administration for the medication exists as tablets which can be taken through oral consumption in the form of tablets and capsules and

sachets and powder. The nano suspensions enable intravenous delivery because their particle size reaches an extremely small dimension which results in 100% bioavailability. (Review on nanocrystals). The study suggests that nanocrystals which possess high drug loading capacity and effective dispersion properties can be used at lower dosages for oral treatment which leads to better patient outcomes and reduced safety risks. [4].

Several articles have been published, discussing the techniques used to synthesize nanocrystal drugs; the type of stabilizers or surfactants involved; and the methods adopted for physicochemical and biological characterization. The highly promising platform needs more research to reach its clinical approval stage. The review assesses nanocrystal drug technology development through its translational research progress. The platform demonstrates clear advantages yet the number of FDA approved products remains extremely low. [5]

II. ADVANTAGES:

- Decreased skin irritation whether administered subcutaneously or intramuscularly. [4]
- The intravenous administration method provides two main advantages which include quick drug dissolution and direct access to specific body tissues. The oral consumption of nanosuspension results in rapid onset reaching higher bioavailability while maintaining a lower fed to fasted ratio. [4]
- The pharmacokinetic performance of the formulation showed improvement. [6]
- The drug can be administered through all routes because of its simple administration and the need for only a small dose which provides fast therapeutic effects. [6]
- The study showed that pharmacokinetic variability decreased through the reduction of fed fasted variability and patient to patient variability. [6]

III. DISADVANTAGES:

- Among potential concerns, measures should be taken to maintain physical stability by checking on sedimentation, as well as compaction. (4)
- Due to inherent product bulkiness and weight, maximum care must be taken while transporting and handling products. (4)
- The production process needs excessive time because nanocrystal production requires time-consuming methods which have high sensitivity during nanocrystal creation and require complete uniform size patterns to achieve success but only achieve 10 production output. (7)
- It is challenging to achieve a uniform and correct dosing. [7]

IV. APPLICATIONS OF NANO CRYSTALS

1. ORAL DELIVERY:

Enhanced Solubility and Dissolution Rates:

Particularly, it must be noted that the use of nanocrystals may have an ability to enhance the solubility of a drug by several orders. The relative solubility of Griseofulvin was 10 times more soluble than the pharmaceutical pure grade. [8]

The development of eplerenone in nanocrystal form achieved a 96.75% dissolution rate which demonstrates the effectiveness of this nanotechnology method for enhancing drug delivery. The nanocrystal products require stabilizers because these substances prevent the product from coagulating or aggregating, which helps sustain its bioavailability properties. Fine-size stable nanocrystals can be produced through the methods of solvent anti-solvent precipitation and emulsion solvent diffusion. [2]

The researchers developed lutein nanocrystals to improve their oral absorption capacity. The nanosuspensions were converted into dry products which were packaged as pellets that were inserted into hard gelatin capsules for their application in nutraceuticals. The produced formulation achieved better in vitro release results which exceeded three to four times the performance of coarse powder. The same lutin nanosuspension was used to create gels and creams after its lyophilization process. The testing of lutein nanocrystals showed that they could penetrate cellulose nitrate membranes fourteen times better than coarse powder. The bai- calein nanocrystal was produced by Zhang Lv et al through a process that combined high pressure homogenisation with anti-solvent recrystallisation. The generated nanocrystals dissolved at a faster rate while their relative bioavailability reached 1.67 times the bioavailability of baicalein crystals.

The fenofibrate nanocrystals were created using the

probe sonication method. The final formulation and pure medication dissolve in 1 sodium lauryl sulphate medium at 73.89 percent and 8.53 percent respectively. The final formulation provided approximately 4.73 times higher relative bioavailability compared to the pure drug formulation. Scientists prepared buparvaquone nanosuspension to create a suspension which they added to hydrogels to enhance their mucoadhesive properties. The study discovered that nanosuspension incorporation into mucoadhesive hydrogels created better physical stability than untrapped nanosuspensions.

The nanosuspension reached the highest dissolution rate during the in-vitro test while the nanosuspension showed better performance than the coarse suspension during the in vivo evaluation. [9]

2. PARENTRAL DRUG DELIVERY:

Nanocrystals increase the effectiveness of drugs that doctors give through multiple injection methods which include intravenous and subcutaneous and intramuscular and intra-articular and intraperitoneal routes. The intravenous delivery of poorly soluble drugs through standard drug distribution systems needs multiple excipients which include co-solvents and surfactants. However, they generate a number of negative responses and raise the dosage volume. [10]

The intraperitoneal route can be used to successfully administer a variety of appropriate nanocrystals. Paclitaxel nanosuspension demonstrated better results than pure taxol for reducing median tumor burden. [11]

3. PULMONARY DRUG DELIVERY:

The pulmonary route of drug delivery enables nanocrystals to provide better tissue adhesion and extended time presence at the site of drug absorption because their dissolution rate matches the requirement for faster drug release. The researchers created curcumin-spray-dried powders for inhalation through the process of wet milling curcumin nanocrystals to develop the product known as curcumin-DPI. The dissolution study showed that curcumin-DPI dissolved at a faster rate than coarse powder. The in vivo tissue distribution investigation revealed that the lung accumulated the majority of the curcumin-DPIs which decreased the amounts in other tissues. Inhalation of curcumin DPIs resulted in a higher plasma concentration because the majority of curcumin DPIs remained in the lung. [12]

Budesonide functions as an anti-inflammatory corticosteroid which scientists developed through the creation of high-pressure homogenisation nanosuspension technology. The combination of tyloxapol (a steric stabiliser) and lecithin (an electrostatic stabiliser) stabilised the budesonide nanosuspension. A commercial nebuliser system operated to transform the created nanosuspension into a nebulisable form. Photon correlation spectrophotometry measurements showed that the nebulised nanocrystals had a particle size of approximately 496 nanometers. The budesonide nanosuspension maintained its stability at room temperature for one year while demonstrating safety and efficacy results in tests with healthy participants. [13]

4. TARGETED DRUG DELIVERY:

The medication reaches its main accumulation point which focuses on a particular treatment area through targeted drug delivery. The targeted drug delivery system uses nanocrystals to demonstrate their ability to bind with specific tissue receptors. The process of targeted medication delivery demands four essential requirements which include containment evasion targeting and release. [14]

Researchers can add various functional groups together with specific ligands to the outside surfaces of nanocrystals. The incorporation of nanocrystals into multiple matrix systems enables researchers to control their movement toward specific body tissues and organs. Chai et al developed RBC-NCs which are drug delivery nanoparticles that use RBC membrane coating to achieve high drug capacity and excellent biocompatibility and long-term stability and extended drug retention. The RBC NC therapies function as cancer treatments which enable the delivery of various medications to patients. [15]

5. SKIN DRUG DELIVERY:

The traditional formulation method fails to work because the active ingredient Nano-crystals create a stronger concentration gradient between the formulation and the skin which makes skin Nanosuspensions more attractive for research. The skin absorption of drugs improves through supersaturated formulations which result from increased saturation solubility. The drug Nano-crystals experience improved stabilization through a positively

charged polymer which increases this specific effect. Drug Nano-crystals show better attraction to negatively charged stratum corneum when their charges exist in opposite states. [16][17][18]

V. PROPERTIES OF NANOCRYSTALS

Enhanced dissolution velocity because of increased surface area:

The Noyes-Whitney equation states that smaller particle dimensions produce more surface area, which increases the rate of dissolution. The process of micronization serves as an effective method to improve bioavailability when the dissolving speed functions as the primary obstacle. Nanonization through micronization increases particle surface area, which results in faster dissolution rates. The rate of dissolution decreases because the compound has low saturation solubility.

Noyes and Whitney Equation:

$Dc/dt = DA/h (Cs-Cx)$

The equation describes how the dissolving rate dc/dt depends on the diffusion coefficient D and the drug particle surface area A and the diffusion layer thickness h and the drug saturation solubility Cs and the drug concentration at a specific time. [19]

INCREASE SATURATION SOLUBILITY:

Nanosized materials exhibit higher saturation solubility and higher kinetic saturation solubility than their micrometre counterparts. The Kelvin equation establishes vapor pressure relationships through the measurement of liquid droplet curvature in gaseous environments. Comparison of nano crystals to micrometre crystals shows that nano crystals produce a more effective supersaturated solution. [20]

INCREASED ADHESIVENESS:

Nano crystals attach themselves to biological mucosa and gastrointestinal mucosa through their natural adhesive properties. The binding of nano crystals which exist in suspension or which result from solid dosage form disintegration occurs through the creation of hydrogen bonds and van der Waals bonds which develop between the particle surfaces and the mucus. The extended retention time of nano crystals enables creation of higher concentration gradients throughout the gastrointestinal tract which results in improved drug absorption and enhanced bioavailability. [21]

IMPROVED STABILITY:

The nanocrystal system exists as a basic formulation which consists of two components: the active pharmaceutical ingredient and the nanosuspension's stabilizing agent and appropriate dispersion medium. The Drug Nano crystal system demonstrates lower chemical reactivity compared to other advanced drug delivery systems which use multiple excipients to create their permanent formulas. [22]

VI. METHODS OF PREPARATION NANOCRYSTALS

1. Top-Down Techniques:

The top-down approach in nanocrystal production represents one of the most widely accepted and industrially scalable methodologies in pharmaceutical nanotechnology, primarily because of its ability to transform poorly soluble drug molecules into nanometer-sized crystals through mechanical energy-driven processes such as media milling and high-pressure homogenization. This approach is fundamentally distinct from bottom-up strategies, as it does not rely on molecular self-assembly or precipitation from solution but instead employs external mechanical forces to reduce the size of preformed drug crystals to the nanoscale. Media milling, often referred to as wet milling, involves dispersing the drug in a stabilizer-containing liquid medium and subjecting it to shear forces generated by grinding beads within a milling chamber. The beads, typically composed of highly durable materials such as zirconium oxide or polymeric composites, collide with drug particles under high agitation, progressively breaking them down into nanocrystals. This technique has been extensively validated for its reproducibility, scalability, and ability to produce stable dispersions, though it requires careful optimization of parameters such as bead size, milling time, and stabilizer concentration to prevent aggregation and ensure uniform particle size distribution. High-pressure homogenization, on the other hand, subjects drug suspensions to extremely high pressures, often exceeding 1500–1700 bar, forcing them through narrow gaps or valves where intense shear forces, cavitation, and particle collision occur, resulting in size reduction to the nano meter range. This method is particularly advantageous for its ability to generate uniform nanocrystals with narrow size distribution and

is compatible with continuous manufacturing processes, making it suitable for large-scale pharmaceutical production. [2]

However, both techniques are energy-intensive, requiring significant mechanical input, and the heat generated during processing can pose risks of drug degradation, necessitating cooling systems or process modifications to preserve drug stability. Despite these limitations, the top- down approach has become the cornerstone of nanocrystal technology in medicine, with several commercial products such as Rapamune® (sirolimus), Emend® (aprepitant), and Tricor® (fenofibrate) successfully developed using these methods, thereby demonstrating their clinical relevance in enhancing solubility and bioavailability of poorly water-soluble drugs. The universality of these techniques lies in their flexibility, as they can be applied to a wide range of drug molecules irrespective of their chemical nature, provided that stabilizers are appropriately selected to prevent recrystallization or particle growth. Moreover, advancements in equipment design, such as the development of nano milling chambers with improved cooling systems and homogenizers with enhanced pressure control, have further expanded the applicability of the top-down approach, enabling the production of nanocrystals with improved stability and reduced processing times. [23]

Recent innovations also include hybrid techniques that combine media milling with homogenization to maximize efficiency and minimize energy consumption, as well as the integration of novel stabilizers such as polymeric surfactants and biocompatible excipients that enhance the long-term stability of nanocrystal formulations. Nevertheless, challenges remain, particularly in terms of scale-up, as laboratory-scale optimization does not always translate seamlessly to industrial-scale production, and issues such as contamination from milling media, batch-to-batch variability, and high operational costs continue to pose obstacles. Additionally, regulatory considerations demand stringent characterization of nanocrystal formulations, including particle size distribution, surface charge, crystallinity, and dissolution profiles, to ensure consistent therapeutic performance and patient safety. Looking forward, the top-down approach is expected to evolve through the incorporation of advanced process analytical technologies (PAT) that allow real-time monitoring and control of particle size during manufacturing, thereby improving reproducibility and reducing waste. Furthermore, coupling these techniques with continuous manufacturing platforms and green chemistry principles may reduce energy consumption and environmental impact, aligning with the pharmaceutical industry's sustainability goals. In conclusion, while the top-down approach is not without limitations, its proven track record in producing clinically successful nanocrystal-based formulations underscores its pivotal role in modern drug delivery systems. By continuously refining process parameters, integrating novel stabilizers, and adopting innovative manufacturing technologies, the pharmaceutical industry can further harness the potential of top-down nanocrystal production to address the persistent challenge of poor drug solubility and bioavailability, ultimately improving therapeutic outcomes and expanding the horizons of nanomedicine. (24)

1.1. Media Milling:

Nanocrystal technology has emerged as a transformative innovation in pharmaceutical sciences, particularly in the enhancement of drug solubility and bioavailability. Among the various top-down approaches employed to produce nanocrystals, media milling has gained prominence due to its efficiency, scalability, and ability to generate stable nanosuspensions. This method, also known as wet milling or bead milling, has been extensively studied and applied in the pharmaceutical industry since the early 1990s, following the pioneering work of Liversidge and colleagues who patented the technology in 1992. Their contribution laid the foundation for the widespread adoption of nanocrystal-based formulations, which have since revolutionized drug delivery systems.

Media milling operates on the principle of mechanical size reduction, wherein coarse drug particles are subjected to intense shear forces and collisions with milling beads inside a milling chamber. The process involves three essential components: the milling chamber, the milling shaft, and the recirculation chamber. These components work synergistically to maintain continuous movement of the drug suspension, ensuring uniform particle size reduction. The milling media, typically composed of strong and dense materials such as yttrium-stabilized zirconium

oxide, stainless steel, glass alumina, titanium, or cross-linked polymers, play a critical role in the process. The choice of bead material and size, which can range from 0.1 to 20 mm, directly influences the efficiency of particle fracture and the final size distribution of the nanocrystals. [4]

During wet media milling, the drug particles, stabilizers, and suitable solvents are introduced into the milling chamber. The stabilizers, often surfactants or polymers, are essential to prevent agglomeration of the newly formed nanocrystals and to maintain the stability of the nanosuspension. As the milling shaft rotates at high speeds, the beads collide with the drug particles, imparting mechanical energy that fractures them into nanosized dimensions. The process is typically conducted under controlled temperature conditions to prevent degradation of thermolabile drugs. The energy input required for particle size reduction is derived from the kinetic energy of the beads, which is transferred to the drug particles through repeated collisions and shear forces. This high-energy environment ensures that even poorly soluble drugs can be reduced to nano meter-scale particles, thereby significantly enhancing their dissolution rate and bioavailability. [25]

One of the major advantages of media milling is its versatility in handling a wide range of drug compounds, including those with poor aqueous solubility. By reducing particle size to the nano meter scale, the surface area of the drug is dramatically increased, leading to improved dissolution kinetics. This enhancement is particularly beneficial for Biopharmaceutics Classification System (BCS) Class II drugs, which are characterized by low solubility and high permeability. Nanocrystals produced via media milling can overcome solubility limitations, enabling more efficient absorption in the gastrointestinal tract and ultimately improving therapeutic outcomes. Furthermore, the nanosuspensions generated through this method can be incorporated into various dosage forms, including oral tablets, capsules, parenteral injections, and topical formulations, thereby expanding their applicability across diverse therapeutic areas.

Despite its advantages, media milling is not without challenges. One of the primary concerns is the potential for contamination from the milling media, especially when beads made of metals or ceramics are used. This issue necessitates careful selection of bead materials and rigorous quality control measures to ensure the purity of the final product. Additionally, the process can be energy-intensive, requiring optimization of milling parameters such as bead size, milling speed, and duration to achieve efficient particle size reduction without excessive energy consumption. Another limitation is the risk of drug degradation due to prolonged exposure to mechanical stress and heat generated during milling. To mitigate these risks, process conditions must be carefully controlled, and stabilizers must be judiciously selected to protect the drug molecules.

Recent advancements in media milling technology have addressed many of these challenges, leading to improved efficiency and product quality. Innovations such as the use of advanced bead materials with higher density and lower contamination risk, as well as the development of closed-loop milling systems with enhanced temperature control, have significantly enhanced the reliability of the process. Moreover, the integration of real-time monitoring techniques, such as laser diffraction and dynamic light scattering, allows for precise control of particle size distribution during milling, ensuring consistent production of nanocrystals with desired characteristics. These advancements have facilitated the commercialization of several nanocrystal-based drug products, including formulations of poorly soluble drugs such as sirolimus, fenofibrate, and itraconazole, which have demonstrated improved bioavailability and therapeutic efficacy. [26]

1.2. High-Pressure Homogenization (HPH):

High-pressure homogenization (HPH) has emerged as one of the most widely adopted and effective top-down techniques for the preparation of pharmaceutical nanocrystals. This method is particularly significant in the field of drug delivery, where poorly water-soluble drugs often face challenges of limited bioavailability. By reducing drug particles to the nano meter scale, HPH enhances solubility, dissolution rate, and ultimately therapeutic efficacy. The process relies on subjecting drug suspensions to extremely high pressures, forcing them through narrow homogenization channels where multiple physical phenomena act simultaneously to break down particles into nanocrystals.

The fundamental principle of HPH involves dispersing crude drug powders in a stabilizing medium, typically aqueous or non-aqueous solutions containing

surfactants or polymers. These stabilizers prevent aggregation and ensure uniform particle size distribution. Once dispersed, the suspension is passed through homogenization chambers under pressures ranging from 1500 to 4000 bar. Within these ultra-thin channels, particle size reduction occurs due to a combination of shear forces, cavitation, and particle collisions. Cavitation, in particular, plays a crucial role: as the liquid experiences rapid pressure drops, vapor bubbles form and collapse violently, generating intense shockwaves that fragment drug particles. This synergistic action of mechanical and hydrodynamic forces results in nanosuspensions with particle sizes typically below 200 nm. [4]

One of the earliest and most influential contributions to HPH technology came from Müller and colleagues, who demonstrated its utility in producing stable nanosuspensions for poorly soluble drugs. Their work highlighted the importance of stabilizers in maintaining dispersion stability and preventing recrystallization. The homogenization gap, typically between 5 and 20 μm, is critical in determining the efficiency of particle size reduction. Narrower gaps increase shear intensity, while wider gaps allow greater turbulence, both contributing to effective homogenization. However, the process must be carefully optimized to avoid excessive energy input, which can lead to drug degradation or destabilization of the suspension.

HPH can be performed in different media, each with distinct advantages and limitations. In aqueous media homogenization, the drug suspension is prepared in water with stabilizers such as surfactants or polymers. This method is relatively straightforward and cost-effective, but it poses challenges for drugs sensitive to hydrolysis. Additionally, the removal of large volumes of water often requires lyophilization, which adds to production costs. In contrast, non-aqueous homogenization employs solvents such as polyethylene glycol (PEG), oils, or ethanol-water mixtures. This approach is particularly useful for drugs unstable in water, as it minimizes hydrolytic degradation. However, cavitation is less efficient in non-aqueous systems due to their higher boiling points, necessitating higher temperatures or specialized techniques such as deep-freeze homogenization.

Micro fluidization represents a specialized variant of HPH, where drug suspensions are forced through microchannels in Z-shaped or Y-shaped homogenization chambers. The design of these chambers ensures that particle collisions occur at extremely high velocities, further enhancing size reduction. Repeated cycles through the microfluidizer are often necessary to achieve the desired particle size, sometimes requiring up to ten passes. While micro fluidization offers precise control over particle size distribution, it is time-intensive and may generate microparticles alongside nanocrystals, necessitating additional processing steps.

Despite its effectiveness, HPH is not without limitations. The process requires significant energy input, which can lead to thermal stress and degradation of heat-sensitive drugs. Stabilizer selection is critical, as inadequate stabilization can result in particle aggregation and loss of nanosuspension stability. Furthermore, the scalability of HPH poses challenges, particularly in maintaining uniform particle size distribution during large-scale production. Nevertheless, continuous advancements in equipment design and process optimization have addressed many of these concerns, making HPH a cornerstone technology in nanocrystal production. [25]

The pharmaceutical applications of HPH-derived nanocrystals are extensive. Drugs such as poorly soluble anticancer agents, antifungals, and cardiovascular therapeutics have been successfully formulated into nanosuspensions using this technique. These formulations exhibit improved dissolution rates, enhanced bioavailability, and reduced variability in therapeutic response. Moreover, nanocrystals produced via HPH can be incorporated into diverse dosage forms, including oral tablets, capsules, parenteral injections, and topical formulations. Their versatility underscores the transformative potential of HPH in modern drug delivery systems.

Recent innovations in HPH technology focus on improving efficiency and reducing processing costs. Advances in homogenizer design, such as the development of ultra-high-pressure systems and improved microfluidizers, have expanded the range of drugs amenable to nanocrystal formulation. Additionally, the integration of HPH with complementary techniques, such as spray drying or freeze drying, has facilitated the production of solid nanocrystal formulations with enhanced stability and ease of handling. Research also explores the use of

novel stabilizers, including biocompatible polymers and natural surfactants, to improve nanosuspension stability and minimize toxicity.

High-pressure homogenization represents a robust and versatile method for producing pharmaceutical nanocrystals. By harnessing the combined effects of shear forces, cavitation, and particle collisions, HPH achieves efficient particle size reduction, thereby enhancing drug solubility and bioavailability. While challenges such as energy requirements and stabilization remain, ongoing advancements continue to refine the technique, solidifying its role as a pivotal technology in nanomedicine. As the demand for effective formulations of poorly soluble drugs grows, HPH is poised to remain at the forefront of nanocrystal production, driving innovation in pharmaceutical sciences. [26]

2. Bottom-up technique (Precipitation method):

The bottom-up technique represents a fundamentally different paradigm in nanocrystal production compared to the top-down approach. Rather than mechanically breaking down larger particles into nanosized forms, the bottom-up method relies on controlled precipitation processes to build nanocrystals from molecular solutions. The principle of this technique is based on dissolving the active pharmaceutical ingredient (API) in a suitable organic solvent, followed by the addition of this solution into a nonsolvent that is miscible with the organic solvent. Under these conditions, and in the presence of stabilizers, the drug molecules precipitate out as nanocrystals. [27]

The stabilizers play a crucial role in preventing uncontrolled growth and aggregation of the particles, thereby ensuring the formation of a stable nanosuspension. The attractiveness of this method lies in its simplicity, relatively low cost, and ease of scale-up, making it appealing for industrial applications. However, the process requires careful optimization of several parameters, including stirring rate, temperature, solvent-to- nonsolvent ratio, drug concentration, viscosity, and the type of stabilizer employed. Each of these factors influences the nucleation and growth kinetics of the nanocrystals, and improper control can lead to heterogeneous particle sizes or instability in the final product. Thus, while bottom-up technology offers significant advantages, it demands precise control of experimental conditions to achieve reproducible and pharmaceutically acceptable outcomes. [28]

VII. CONTROL FLOW CAVITATION (CFC)

Control Flow Cavitation (CFC) has emerged as one of the most advanced and efficient technologies for the production of nanocrystals in pharmaceutical sciences. Unlike conventional cavitation processes, which often generate uncontrolled destructive forces, CFC is designed to regulate the size, density, location, and intensity of bubble implosions within a cavitation zone. This precise control transforms cavitation into a constructive process, releasing high-intensity energy that can be harnessed to reduce drug particles to nanoscale dimensions with remarkable uniformity. The ability to achieve desired particle size distributions is critical in pharmaceutical nanocrystal technology, as particle size. [29]

CFC ensures that nanocrystals produced through this method maintain consistent physicochemical properties across multiple batches, which is essential for clinical translation and regulatory approval. The scalability of CFC also addresses one of the major challenges in nanocrystal production, bridging the gap between laboratory-scale innovation and industrial-scale manufacturing, thereby making it a promising tool for modern drug development. [30]

Beyond its fundamental role in particle size reduction, CFC technology offers significant advantages in process control, efficiency, and adaptability. Specialized CFC chamber designs allow customization for hydrodynamic, chemical, biomedical, and pharmaceutical applications, enabling researchers to optimize conditions for drug stability and therapeutic performance. The controlled cavitation environment not only facilitates the formation of nanocrystals but also allows the incorporation of stabilizers and excipients during production, thereby improving stability and preventing aggregation or Ostwald ripening. [31]

This opens new opportunities for developing advanced drug delivery systems, including targeted therapies and formulations with enhanced pharmacokinetic and pharmacodynamic profiles. Recent research has demonstrated that CFC-generated nanocrystals can be tailored for site-specific delivery, offering potential breakthroughs in the treatment of cancer, neurological disorders, and infectious diseases. While challenges

such as long-term stability and regulatory acceptance remain, the reproducibility, scalability, and efficiency of CFC position it as a transformative technology in pharmaceutical nanocrystal production. As innovations continue to refine this process, CFC is expected to play a pivotal role in advancing nanomedicine and shaping the future of pharmaceutical sciences. [32]

Spray Drying:

Spray drying has emerged as one of the most versatile and widely adopted techniques for the preparation of pharmaceutical nanocrystals, owing to its ability to transform liquid feedstocks such as solutions, emulsions, suspensions, and slurries into dry powders in a single, continuous step. The process involves atomizing the liquid into fine droplets, which are rapidly dried by a stream of hot gas, resulting in solid particles with controlled size and morphology. Traditional spray drying systems, however, have been limited in their efficiency of collecting particles below 5 μm due to constraints in cyclone separator technology. To overcome these limitations, advanced systems such as piezoelectric-driven vibrating mesh atomizers and electrostatic powder collectors have been introduced, significantly improving yield and enabling the production of nanocrystals with narrow size distribution. The development of the Nano Spray Dryer B-90 by Büchi (Switzerland) represents a notable advancement in this field, as it allows precise control over particle size and morphology, making it particularly suitable for nano- crystallization of poorly soluble drugs. This innovation has facilitated the preparation of solid dispersions and suspensions at the nanoscale, thereby enhancing drug solubility, dissolution rate, and ultimately bioavailability.

Beyond its technical efficiency, spray drying offers remarkable adaptability and scalability, making it highly relevant for both laboratory-scale research and industrial-scale pharmaceutical production. The process can be tailored to accommodate heat-sensitive as well as heat-resistant compounds, with feedstocks ranging from solutions and gels to melts and suspensions. Furthermore, the integration of polymeric dispersants during spray drying enables the formation of solid solutions or submicron suspensions, which stabilize nanocrystals and prevent agglomeration. The rapid drying kinetics and continuous nature of the process ensure reproducibility and consistency in particle characteristics, while the availability of automated control systems enhances precision and reduces variability. In the context of nanotechnology, spray drying has become increasingly important as the demand for nanoparticles with high yield, controlled morphology, and uniform size distribution continues to grow. Its ability to produce nanocrystals with improved dissolution properties and enhanced pharmacokinetic profiles underscores its significance in modern drug delivery systems, positioning spray drying as a cornerstone technology in the advancement of nanocrystal-based therapeutics. [33]

Supercritical Fluid:

Supercritical fluid technology, particularly the supercritical antisolvent (SAS) process, has emerged as a promising approach for the preparation of nanocrystals in pharmaceutical sciences. In this method, a solute dissolved in an organic solvent is rapidly precipitated upon exposure to a supercritical fluid, most commonly supercritical carbon dioxide, which acts as an antisolvent. The unique physicochemical properties of supercritical fluids, such as their tunable density, diffusivity, and solvating power, enable the generation of extremely high supersaturation conditions. This rapid supersaturation leads to the formation of nanosized particles with controlled morphology and narrow size distribution, which are difficult to achieve with conventional antisolvent precipitation techniques. The SAS process offers distinct advantages, including the ability to completely remove residual solvents, precise control over particle characteristics by adjusting pressure and temperature, and the potential to incorporate habit modifiers or growth inhibitors to tailor crystal properties. These features make supercritical fluid-based nanocrystal production highly attractive for enhancing drug solubility and dissolution rates, particularly for poorly water-soluble compounds.

Recent advancements in the application of supercritical fluids in nanocrystal technology have demonstrated their versatility in producing stable and bioavailable drug formulations. Researchers have successfully employed SAS to precipitate drugs such as sulfathiazole and griseofulvin, using additives like urea and poly (sebacic anhydride) to modulate crystal growth and prevent agglomeration. The process not only ensures uniform particle size but also enhances

the dissolution profile and bioavailability of hydrophobic drugs, thereby improving their therapeutic efficacy. Moreover, the environmentally friendly nature of supercritical fluids, especially carbon dioxide, aligns with the growing emphasis on sustainable pharmaceutical manufacturing. Despite challenges such as scalability and the need for specialized equipment, the SAS technique continues to gain recognition as a cutting-edge method for nanocrystal production. Its ability to generate high-quality nanoparticles with reproducible characteristics positions supercritical fluid technology as a vital tool in the development of next-generation drug delivery systems, offering significant potential for advancing modern therapeutics. [33]

Emulsion Polymerization:

The emulsion polymerization method represents a distinctive approach to the preparation of pharmaceutical nanocrystals, particularly suited for laboratory-scale investigations. In this technique, an oil-in-water (O/W) emulsion is initially created by dissolving the active pharmaceutical ingredient (API) in volatile organic solvents or partially miscible solvents with water, which serves as the dispersion phase. Stabilizers are employed to emulsify the system, ensuring uniform droplet formation and preventing coalescence. Following emulsification, the volatile solvents are evaporated, and the resulting dispersion is subjected to mixing and extraction processes to yield drug nanocrystals. The physicochemical quality of the final nanocrystal product is highly dependent on several critical parameters, including the type and concentration of emulsifier, the stirring rate, the rate of solvent evaporation, the temperature gradient maintained during processing, and the pH of the medium. Each of these factors influences the size distribution, stability, and crystallinity of the nanocrystals, thereby determining their suitability for pharmaceutical applications.

Despite its utility in producing nanocrystals with desirable properties, the emulsion polymerization method is largely restricted to laboratory-scale production due to its reliance on homogenization or ultrasonic techniques, which pose challenges for scalability. The method requires precise control over process variables, and its dependence on volatile organic solvents raises concerns regarding environmental safety and regulatory compliance. Nevertheless, it has proven effective in generating nanocrystals of certain drugs, such as florfenicol, where enhanced solubility and bioavailability were achieved. The technique's ability to produce uniform nanocrystals with controlled particle size makes Vindustrial-scale production remains limited, necessitating further innovations in process engineering and solvent management to overcome these barriers. Thus, while emulsion polymerization continues to be a promising laboratory tool for nanocrystal development, its broader application in pharmaceutical manufacturing requires significant technological advancements. [4]

VIII. Nano-crystal Preparation Using Nano-porous Materials

Nanocrystal preparation using nano-porous materials represents one of the most innovative and efficient approaches in modern pharmaceutical nanotechnology. This method exploits the unique structural characteristics of nano-porous carriers, which possess highly ordered pore networks capable of confining drug molecules at the nanoscale. By introducing active pharmaceutical ingredients (APIs) into these pores, nanocrystals can be formed with controlled size and morphology, thereby enhancing their physicochemical properties. Materials such as mesoporous silica, controlled pore glass (CPG), porous polymers, and metal-organic frameworks have been extensively investigated for this purpose due to their tunable pore diameters, high surface areas, and chemical stability. The process typically involves filling the pores with a drug solution, followed by solvent evaporation or precipitation, leading to the nucleation and growth of nanocrystals within the confined spaces. This confinement effect restricts crystal growth, resulting in uniform nanocrystals with improved solubility and dissolution rates compared to bulk drug particles. The Washburn equation has been applied to predict and optimize the capillary flow of drug solutions into porous channels, ensuring complete pore filling and efficient nanocrystal formation. Such a technique not only provides precise control over particle size but also minimizes agglomeration, a common challenge in conventional nanocrystal preparation methods. [34]

Recent advancements in this area have demonstrated

the versatility of nano-porous materials as carriers for poorly water-soluble drugs, offering significant improvements in bioavailability and therapeutic efficacy. For instance, O'Mahony and colleagues developed a method to load APIs into controlled pore glass, achieving reproducible nanocrystal formation with enhanced dissolution profiles. The ability to engineer nanocrystals directly within the pores of these materials has opened new avenues for drug delivery, particularly in oral formulations where solubility limitations often hinder clinical performance. Moreover, nanostructured lipid carriers and porous polymers such as polystyrene and polycyclohexyl ethylene have been explored to combine the benefits of lipid-based solubilization with the structural confinement of porous matrices. These hybrid systems not only stabilize nanocrystals but also provide controlled release properties, thereby improving pharmacokinetic behavior. The nano-porous approach is considered revolutionary because it simplifies the preparation process, reduces the need for complex milling or homogenization techniques, and offers scalability for industrial applications. As research progresses, the integration of nano-porous carriers with advanced drug delivery strategies is expected to further enhance the therapeutic potential of nanocrystals, making this method a cornerstone in the future of pharmaceutical nanotechnology. (35)

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