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A REVIEW ON STUDY OF DRUG NANOCRYSTAL TECHNIQUE

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❖ **Abstract:** Most of the recently developed new chemical entities are poorly water soluble and they create major problems during formulation and development of new dosage form and due to poor solubility and poor bioavailability. The drugs belong to BCS class II and class IV has problem of solubility, to overcome the solubility problem nanotechnology is most useful technique. In this review article the main focus on Nanocrystals and various techniques used for preparation of Nanocrystals. Drug nanocrystals consists pure poorly water soluble drugs without any matrix material which means that it is carrier free drug delivery. Nanocrystals technologies have been introduced as advantageous, universal formulation approaches for the BCS class II and IV drugs. Nanocrystals, with greater surface to volume ratio, can effectively increase both the dissolution rate and saturation solubility of active ingredients The Nanocrystals is suitable drug delivery system for all commonly used routes of administration such as oral, IV, SC, and IM and topical application. Nanocrystals can also be incorporated into the tablets, capsules, fastmelts and lyophilized for sterile product applications. There are no of techniques which are used for production including precipitation, milling, high pressure homogenization and combination methods such as Nano-Edge, SmartCrystal and Precipitation-lyophilization-homogenization (PLH) technology.

Keywords: Nanotechnology, nanocrystals, techniques of production of nanocrystals, Solubility.

❖ INTRODUCTION:

Nanotechnology has been increasingly applied in the field of drug delivery to address challenges associated with the poor water solubility of certain drugs, especially hydrophobic ones. This issue is significant because the human body is primarily composed of water, and drugs need to be in a soluble form to be effectively absorbed and distributed.

Nanotechnology-based drug delivery systems offer several advantages in this context:

1. **Improved Solubility:** Nanoparticles can encapsulate hydrophobic drugs, enhancing their solubility in water. This allows for better absorption and distribution in the body.

2. **Enhanced Bioavailability:** By improving solubility, nanotechnology helps increase the bioavailability of drugs. This means that a larger proportion of the administered dose reaches the target site, leading to better therapeutic outcomes.

3. **Targeted Delivery:** Nanoparticles can be designed to target specific cells or tissues. This targeted drug delivery minimizes side effects by ensuring that the therapeutic agent reaches the intended site while sparing healthy tissues.

4. **Controlled Release:** Nanocarriers can provide controlled and sustained release of drugs over time. This allows for a more stable and prolonged therapeutic effect, reducing the frequency of dosing.

5. **Protection of Drugs:** Nanoparticles can protect drugs from degradation, metabolism, or elimination before reaching their target site. This can improve the stability and effectiveness of certain drugs.

Common nanocarriers used in drug delivery include liposomes, micelles, dendrimers, and nanoparticles. These carriers can be engineered to have specific properties, such as size, surface charge, and surface modifications, to optimize drug delivery.

The application of nanotechnology in drug delivery has the potential to revolutionize the pharmaceutical industry by addressing formulation challenges and improving the efficacy of a wide range of therapeutic agents.[1]

1. **Issue of Poor Solubility:** Drugs with low solubility, especially those classified under Class II of the Biopharmaceutical Classification System (BCS), face challenges related to low oral bioavailability and erratic absorption.

2. **Dissolution Velocity as a Rate-Limiting Step:** In Class II drugs, the rate-limiting step for absorption is often the dissolution velocity due to low solubility. Despite high permeability, poor solubility leads to a limited concentration gradient between the gastrointestinal tract and the bloodstream, hindering drug transport and oral absorption.

3. **Challenges with Conventional Formulations:** Conventional formulations of poorly water-soluble drugs frequently result in poor and highly variable bioavailability. Factors such as the fed–fasted state of the patient can impact the performance of the dosage form, leading to suboptimal dosing and slower-than-anticipated onset of action.

4. **Importance of Improving Solubility:** Enhancing drug solubility is crucial for improving bioavailability, and it is considered one of the most challenging tasks in drug development.

5. **Approaches to Increase Solubility:** Strategies for increasing solubility are categorized into physical and chemical modifications.

- **Physical Modifications:** Techniques include decreasing particle size (micronization, nanonization), forming polymorphs/pseudo polymorphs, complexation/solubilization (using surfactants or cyclodextrins, conjugation to dendrimers, addition of co-solvents), and preparing drug dispersions in carriers (eutectic mixtures, non-molecular solid dispersions, solid solutions).

- **Chemical Modifications:** This involves the synthesis of soluble prodrugs and salts.

6. **Micronization vs. Nanonization:** While micronization increases surface area, nanonization takes it a step further by producing drug nanocrystals. Nanonization is highlighted as a method to improve saturation solubility, leading to increased dissolution rates and absorption.[2]

❖ SATURATION SOLUBILITY VS DISSOLUTION VELOCITY:

It seems like you've provided information about the definitions of "dissolution" and "dissolution rate" according to IUPAC 1997. Let's break down the key points:

1. Dissolution:

- Defined as the mixing of two phases (e.g., drug and dissolution medium) with the formation of a new homogeneous phase, which is a solution.

- During dissolution, the distinct boundary between the drug and the dissolution medium disappears**.**

2. Dissolution Rate:

- Defined as the change in dissolved drug concentration over a specific period of time.

- Mathematically expressed as dc/dt where *c* is the concentration of the dissolved drug, and *t* is time.

- In simple terms, it represents the speed at which drug molecules or ions enter the liquid media (solution) per unit time.

The last statement you provided suggests that when it is claimed that a particular method or dosage form increases the dissolution rate, it means that it enhances the speed at which drug molecules enter the liquid media (solution).

Now, regarding nanocrystals, the initial statement suggests there might be confusion about the relationship between nanocrystals and their ability to increase solubility versus dissolution velocity. Generally, nanocrystals are known to have increased surface area compared to larger particles, which can lead to improved dissolution rates. This is due to the higher surface area providing more sites for interaction with the dissolution medium.[3]

1. **Dissolution Rate Comparison:**

- The goal is to compare the dissolution rates of two formulations.
- Dissolution rate refers to the speed at which a substance (e.g., drug molecules) dissolves in a liquid medium (dissolution media).

2. **Dissolution Profile Measurement:**

- Dissolution profiles of the two formulations are measured.
- A dissolution profile is a representation of how the concentration of a substance (e.g., drug) changes over time as it dissolves in a particular medium.

3. **Same Dissolution Media:**

- The measurements are conducted in the same dissolution media for both formulations.
- This ensures a consistent environment for the comparison, eliminating the potential influence of different dissolution media on the results.

4. **Maximum Dissolution Limit:**

- The formulation that reaches the maximum dissolution limit quickly is considered to have a high dissolution rate or velocity.
- The maximum dissolution limit represents the highest concentration of the substance that can be dissolved in the given dissolution media under the specified conditions.[4]

Solubility Definition:

According to IUPAC, solubility is defined as "the analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent."

In simpler terms, solubility refers to the maximum amount of a drug (solute) that can be dispersed at the molecular level into a specific medium (solvent) under defined temperature and pressure conditions.

Saturation Solubility:

The specific concentration beyond which the solvent can no longer accommodate more solute molecules is defined as the "saturation solubility" of the particular solute.

Saturation solubility represents the point at which the solvent is saturated with the maximum amount of solute it can dissolve under the given conditions.[5]

1.**Time and Saturation Solubility:**

- The definition of solubility does not explicitly mention the time it takes to reach saturation.
- To measure saturation solubility accurately, sufficient time must be given for the solute and solvent to reach the stage of "thermodynamic equilibrium."

2. **Thermodynamic Equilibrium:**

- Thermodynamic equilibrium is a state where the amount of drugs dissolved is equal to the amount of drugs re-precipitated in unit time.
- Achieving thermodynamic equilibrium is crucial for obtaining reliable and meaningful saturation solubility data.

3. **Shake-Flask Method:**

- The most widely used and reliable method to measure saturation solubility is the shake-flask method.
- In this method, excess solid (solute) is added to a medium (solvent), and the mixture is shaken for approximately 24 to 48 hours.
- The extended shaking time ensures that there is complete equilibrium between the solute and the solvent, allowing accurate determination of saturation solubility.[6]

1.Equilibrium Achievement:

Once thermodynamic equilibrium is achieved by shaking the solute and solvent for an extended period (24 to 48 hours), the system is considered stable.

2.Supernatant Analysis:

The supernatant, which is the liquid portion after the shaking process, is removed.

It is then passed through a 0.45 µm filter to remove any undissolved solids or particulate matter.

3.Concentration Analysis:

The filtered supernatant is analyzed for the concentration of the solute.

This analysis provides information about the maximum amount of solute that has dissolved in the solvent under the given conditions.

4.Characterization of Undissolved Solids:

Undissolved solids are characterized using analytical methods such as Differential Scanning Calorimetry (DSC) and powder X-ray diffraction.

DSC helps in studying thermal properties, and powder X-ray diffraction is used to examine the crystalline structure of the undissolved solids.

This characterization is important to ensure that the system has not undergone any polymorphic changes (changes in the arrangement of molecules in the solid state), which could affect the interpretation of saturation solubility data.

❖ ADVANTAGES OF NANOCRYSTALS

• Suitable for administration via any route.

• Improved drug solubility and bioavailability.

• Reduced tissue irritation in subcutaneous or intramuscular administration.

• Rapid dissolution and tissue targeting possible through IV administration.

• Oral administration of nanosuspensions results in rapid onset, reduced fed/fasted ratio, and enhanced bioavailability.

• Particle size reduction increases absorption within the absorption window.

• Suitable for incorporation into tablets, pellets, hydrogels, and suppositories for various administration routes.

• Increasing amorphous fraction in particles may induce a potential change in crystalline structure and enhance solubility.

• Potential for surface modification of nanosuspension for site-specific delivery.

• Achievable higher drug loading.

• Long-term physical and chemical stability due to the absence of Ostwald ripening [7,8].

❖ DISADVANTAGES OF NANOCRYSTALS

• Challenges may arise from physical stability, sedimentation, and compaction.

• Due to its bulkiness, careful handling and transport are necessary.

• Achieving uniform and accurate dosing may be challenging [7,8]

❖ PROPERTIES OF NANOCRYSTALS

Increase of dissolution velocity by surface area enlargement

Reducing the size results in a larger surface area, consequently leading to an elevated dissolution rate, as per the Noyes-Whitney equation. Thus, micronization proves effective in improving the bioavailability of drugs when the dissolution rate acts as the limiting factor. Advancing from micronization to nanonization further amplifies the particle surface, thereby enhancing the dissolution rate. Generally, a low dissolution rate is associated with low saturation solubility. This relationship is encapsulated by the Noyes and Whitney Equation.

$$\frac{dc}{dt} = \frac{DA}{h}(Cs - Cx)$$

In this context, where dc/dt represents dissolution velocity, D denotes the diffusion coefficient, A stands for the surface area of the drug particle, h is the thickness of the diffusional layer, Cs represents the saturation solubility of the drug, and Cx indicates the concentration in the surrounding liquid at a given time.

Increase in saturation solubility

The saturation solubility Cs remains a constant dependent on the compound, dissolution medium, and temperature. This holds true for powders encountered in daily life with a size in the micrometer range or larger. However, when the particle size falls below a critical threshold of 1–2 μm, the saturation solubility becomes a variable influenced by the particle size. It exhibits an upward trend with diminishing particle size below 1000 nm. Consequently, drug nanocrystals exhibit an augmented saturation solubility.

This offers two distinct advantages:

i. According to Noyes and Whitney equation, the dissolution velocity is further enhanced because dc/dt is proportional to the concentration gradient (Cs−Cx)/h (Cs- saturation solubility, Ct - bulk concentration, h-diffusional distance).

ii. ii. Due to the increased saturation solubility the concentration gradient between gut lumen and blood is increased, consequently the absorption by passive diffusion.

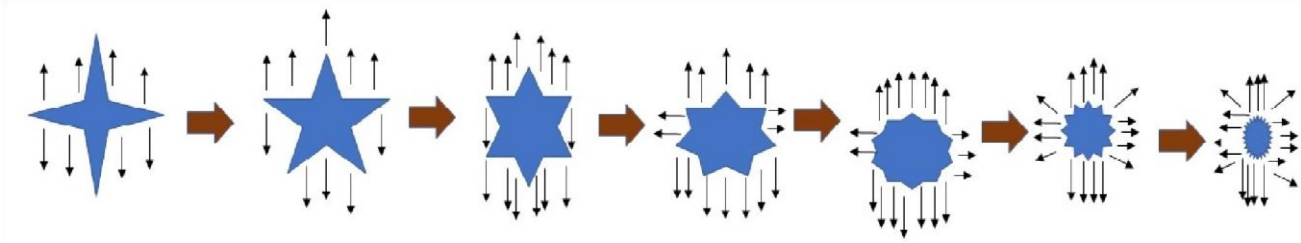

Fig. (1). Reducing the particle size, increases the curvature of the particle and so is the dissolution velocity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

❖ TECHNIQUES FOR MANUFACTURING OF NANOCRYSTALS:

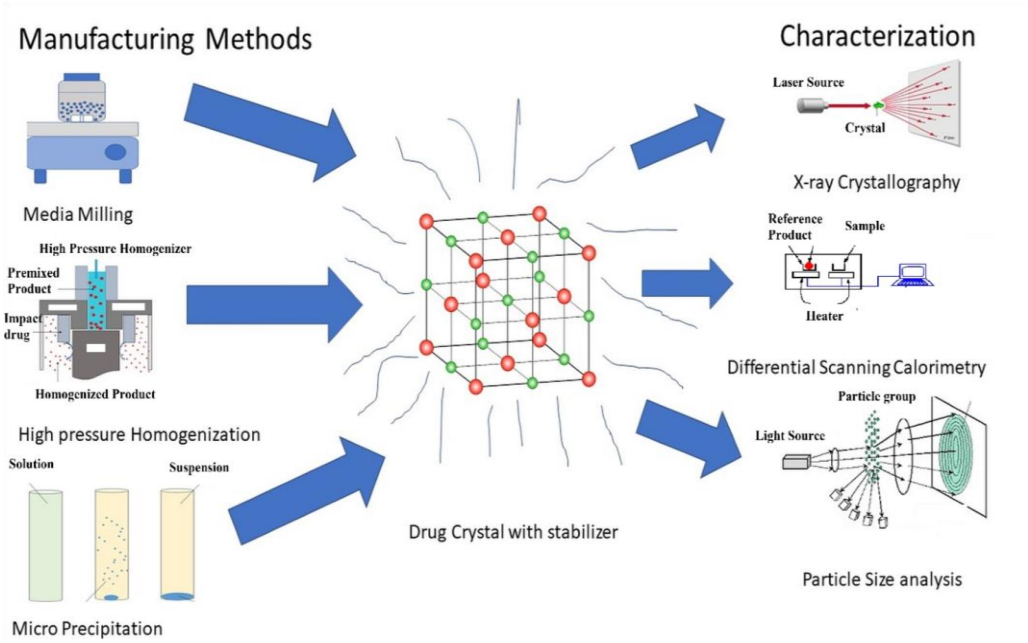

Fig. (2). methods for manufacturing nanocrystals along with characterization techniques.

(a higher resolution / colour version of this figure is available in the electronic copy of the article)

1. Bottom up technology:

1.1 Anti-solvent precipitation

1.2 Utilization of supercritical fluids

1.3 Spray-drying

2. Top down Technology:

2.1 Media milling

2.1.1. Bead milling

2.1.2. Dry co-grind

2.2 High pressure homogenizations:

2.2.1. Homogenization in Aqueous media (Disso cubes)

2.2.2. Homogenization in Non Aqueous Media (Nanopure)

2.2.3 Nanojet technology

2.3 Emulsion solvent diffusion method

3. Combination technology:

3.1 NANOEDGE® Technology

3.2 SmartCrystal® Technology

4. Other methods:

4.1. Solvent evaporation

4.2. Sonocrystallization

4.3. Melt emulsification

4.4. Bottom-Up NanoCrySP Technology

1. Bottom up technology:

The principle of this technology is grounded in precipitation, wherein the drug is dissolved in a solvent and subsequently introduced to a non-solvent. This introduction of the solvent to a non-solvent induces the precipitation of fine drug particles**.**

1.1Precipitation technology (Antisolvent method):

In this technique, the drug is dissolved in an organic solvent where it is soluble, and this solution is blended with a miscible antisolvent to induce precipitation in the presence of a stabilizer. In the water-solvent mixture, the solubility is low, prompting the drug to precipitate. High shear processing can be integrated with precipitation by combining rapid precipitation with high-pressure homogenization. Baxter Healthcare introduced the patented technology US 6,884,436, known as NANOEDGE, which relies on the precipitation of friable materials for fragmentation under conditions of high shear and/or thermal energy.

The process involves the sudden super saturation of the mixed solution through the rapid addition of the drug solution to the antisolvent, leading to the generation of fine crystalline or amorphous solids. Amorphous material precipitation may be favored at high supersaturation when the solubility of the amorphous state is exceeded.

The precipitation method finds application in preparing amorphous drug nanoparticles, as exemplified by carotene nanoparticles in the food industry, such as Lucarotin® or Lucantin® (BASF). In this process, a solution of the carotenoid, along with a surfactant in a digestible oil, is mixed with an appropriate solvent at a specific temperature. The addition of a protective colloid forms a solution, resulting in an O/W two-phase system. The carotenoid, stabilized by the colloid, localizes in the oily phase. Subsequent lyophilization, as confirmed by X-ray analysis, reveals that approximately 90% of the carotenoid is in an amorphous state [8]

1.2 Supercritical fluid methods:

Nanoparticles can be generated through various methods, including the Rapid Expansion of Supercritical Solution (RESS) process, Supercritical Antisolvent process, and Precipitation with Compressed Antisolvent (PCA) process. In the RESS technique, a drug solution is expanded through a nozzle into a supercritical fluid, causing the drug to precipitate as fine particles due to the loss of solvent power of the supercritical fluid. Young et al. utilized this technique to prepare cyclosporine nanoparticles with diameters ranging from 400 to 700 nm.

In the PCA method, the drug solution is atomized into a CO2 compressed chamber. As solvent removal takes place, the solution becomes supersaturated, leading to precipitation. In the Supercritical Antisolvent process, the drug solution is injected into the supercritical fluid, resulting in solvent extraction and the drug solution becoming supersaturated.

However, these methods have some drawbacks, such as the use of hazardous solvents and higher amounts of surfactants and stabilizers compared to other techniques.

1.3 Spray drying:

This method is commonly employed for drying solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom and dried in the same direction by hot air, resulting in the formation of spherical particles. Spraying is accomplished using an atomizer that rapidly rotates, causing the solution to scatter due to the centrifugal effect. The solution, at a specified flow rate, is directed to the inner tube with a peristaltic pump, while nitrogen or air at a constant pressure is supplied to the outer tube. Spraying is facilitated by a nozzle.

The droplets of the solution become significantly small during spraying, leading to an increased surface area of the drying material and, consequently, fast drying. The concentration, viscosity, temperature, and spray rate of the solution can be adjusted to optimize particle size, fluidity, and drying speed. This method has been effective

in enhancing the dissolution rate and bioavailability of various drugs, including hydrocortisone and the COX-2 inhibitor (BMS-347070) [9].

2 Top down technolog:

Disintegration methods, categorized as "Top-down Technologies," are favored over precipitation methods.

2.1 Media milling (Nanocrystals or Nano systems)

2.1.1. Bead milling:

Originally developed by Liversidge et al., this method involves the production of nanosuspensions using high-shear media mills or pearl mills. The media mill comprises a milling chamber, a milling shaft, and a recirculation chamber. Shear forces of impact, generated by the movement of the milling media, result in particle size reduction. The milling medium, made of materials like glass, zirconium oxide, or highly cross-linked polystyrene resin, is fed into the milling chamber along with water, drug, and stabilizer. The milling media or pearls are then rotated at an exceptionally high shear rate under controlled temperatures.

Nanosuspensions or nanoparticles are formed due to the high energy and shear forces resulting from the impaction of the milling media with the drug. This imparts the necessary energy input to break down micro-particulate drug into nano-sized particles. The media milling procedure is effective for both micronized and non-micronized drug crystals. To minimize impurities caused by erosion of the milling media, the milling beads are coated.

Two fundamental milling principles are employed: either the milling medium is moved by an agitator, or the entire container undergoes a complex movement, leading to a corresponding motion of the milling media. The milling time varies based on factors such as surfactant content, drug hardness, viscosity, temperature, energy input, and the size of the milling media. The milling duration can range from approximately 30 minutes to several hours or even days [10].

2.1.2. Co-grinding:

Stable nanosuspensions are created by formulating poorly soluble drugs with soluble polymers and copolymers through the dry grinding process, following dispersion in a liquid medium. Colloidal particle formation is achieved for numerous poorly water-soluble drugs, including griseofulvin, glibenclamide, and nifedipine, by grinding them with polyvinylpyrrolidone (PVP) and sodium dodecyl sulfate (SDS). Various soluble polymers and copolymers, such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives, have been employed in this method. Utilizing dry co-grinding improves the physicochemical properties and dissolution of poorly water-soluble drugs by enhancing surface polarity and inducing a transformation from a crystalline to an amorphous state. This method is advantageous for its ease, cost-effectiveness, and the absence of a need for organic solvents.

2.2 High Pressure Homogenization

When producing nanocrystals using homogenization methods, three notable technologies stand out: Microfluidizer technology (Nanojet technology), Piston gap homogenization in aqueous media (Dissocubes® technology), and in water mixtures or in non-aqueous media (Nanopure® technology) [11, 2]

2.2.1. Microfluidizer Technology (Nanojet technology)

This technology is referred to as opposite stream or Nanojet technology. It involves the use of a Microfluidizer, which utilizes a chamber where a suspension stream is divided into two or more parts that collide with each other at high pressure. This collision induces particle collision, shear forces, and cavitation forces.

The process generates high shear forces due to particle collision and high pressure, leading to particle size reduction. Equipment employing this principle includes the M110L and M110S microfluidizers. Dearn utilized the microfluidization process to prepare nanosuspensions of atovaquone.

A notable drawback of this technique is the requirement for a high number of passes through the microfluidizer, and the resulting product may contain a relatively larger fraction of microparticles.

2.2.2. Piston gap homogenization in aqueous media (Dissocubes)

This technology, developed by R.H. Muller in 1999, initially held a patent by DDS GmbH and was later transferred to Skype Pharmaceuticals. Commonly used homogenizers include the APVMicron Lab 40 (APV Deutschland GmbH, Lubeck, Germany) and piston-gap homogenizers. In this method, a suspension containing a drug and surfactant is pressurized and forced through a nanosized aperture valve in a high-pressure homogenizer. The particle size reduction in this method relies on the cavitation principle.

The dispersion, present in a 3cm diameter cylinder, is rapidly passed through a very narrow gap of 25µm. According to Bernoulli's law, the flow volume of liquid in a closed system per cross-section remains constant, leading to an increase in dynamic pressure and a decrease in static pressure below the boiling point of water as the diameter decreases from 3cm to 25µm. Consequently, water begins boiling at room temperature, forming gas bubbles that implode when the suspension exits the gap (a phenomenon known as cavitation), reaching normal air pressure. The cavitation forces are sufficiently high to convert drug microparticles into nanoparticles. The final particle size of drug nanocrystals in this method is influenced by the power density of the homogenizer, the number of homogenization cycles, temperature, and homogenization pressure.

2.2.3 Homogenization in Non Aqueous Media (Nanopure)

In this technology suspension is homogenized in water-free media or water mixtures. In the Dissocubes technology the cavitation is the principle determining factor of the process oils and oily fatty acids have very low vapour pressure and a high boiling point as compare to water. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by highpressure homogenization mention that higher temperatures of about 80°C promoted disintegration, which cannot be used for thermo labile compounds. In Nanopure technology, the drug suspensions in the non aqueous media were homogenized at 0°C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to Dissocubes and hence can be used effectively for thermo labile substances at milder conditions. [2]

2.3. Emulsion solvent diffusion method

The utilization of emulsions as templates is suitable for drugs soluble in volatile organic solvents or partially water-miscible solvents. These solvents can serve as the dispersed phase of the emulsion. An organic solvent or a mixture of solvents, loaded with the drug, is dispersed in an aqueous phase containing suitable surfactants through stirring to create an emulsion. The resulting emulsion is further homogenized using high-pressure homogenization. After several homogenization cycles, the emulsion is diluted with water and homogenized once more to disperse the organic solvent and transform the droplets into solid particles.

As each particle is formed within an emulsion droplet, the particle size of the nanosuspension can be controlled by managing the size of the emulsion. Optimizing the surfactant composition enhances the absorption of the organic phase, ultimately increasing the drug loading in the emulsion. While originally methanol, ethanol, ethyl acetate, and chloroform were used as organic solvents, concerns about environmental hazards and human safety have limited their routine use in manufacturing processes. This method has been employed to prepare nanosuspensions of ibuprofen, diclofenac, and acyclovir**.**

3. Patented / Combination Technologies :

3.1 NANOEDGE™:

The foundational principles of NANOEDGE align with those of precipitation and homogenization. The combination of these techniques results in a smaller particle size and enhanced stability within a shorter timeframe. NANOEDGE technology effectively addresses a significant drawback of the precipitation technique, particularly crystal growth and long-term stability issues. In this method, the precipitated suspension undergoes additional homogenization, leading to a reduction in particle size and prevention of crystal growth.

The precipitation step is carried out in water using water-miscible solvents like methanol, ethanol, and isopropanol. While it is preferable to completely eliminate these solvents, they can be tolerated to a certain extent in the formulation. For the efficient production of nanosuspensions using NANOEDGE technology, an evaporation step can be incorporated to yield a solvent-free modified starting material, followed by high-pressure homogenization [13].

3.2 SmartCrystal® technology:

This technology was initially developed by PharmaSol GmbH and later acquired by Abbott. It constitutes a toolbox of various combination processes, allowing for the selection of process variations based on the physical characteristics of the drug, such as hardness. In Process H42, nanocrystals are prepared through a combination of spray-drying and high-pressure homogenization (HPH) within a few homogenization cycles. Processes H69 (Precipitation and HPH) and H96 (Lyophilization and HPH) produce nanocrystals of amphotericin B within a size range of about 50 nm.S. Kobierski et al. (2008) employed a two-step process involving pre-milling followed by high-pressure homogenization (HPH) to produce nanocrystals. Nanosuspensions of the cosmetic active hesperidin were generated using both ball milling and combination processes. The nanosuspensions prepared using SmartCrystal® technology exhibited a smaller size, indicating better physical stability during storage [13].

4.Other technologie:

4.1Solvent Evaporation:

In this method, polymer solutions are prepared in volatile solvents and emulsions. Over the past few years, dichloromethane and chloroform were commonly used, but these have now been replaced by ethyl acetate due to its improved toxicological profile. The emulsion is transformed into a nanoparticle suspension through the evaporation of the polymer solvent, allowing it to diffuse through the continuous phase of the emulsion.

Conventional methods employ two main strategies for emulsion formation: the preparation of single emulsions, such as oil-in-water (o/w), or double emulsions, such as (water-in-oil)-in-water, (w/o)/w. These methods involve high-speed homogenization or ultrasonication, followed by solvent evaporation either through continuous magnetic stirring at room temperature or under reduced pressure. Solidified nanoparticles are collected via ultracentrifugation, washed with distilled water to remove additives like surfactants, and then lyophilized. The particle size is influenced by the concentration of the polymer, stabilizer, and the speed of the homogenizer.

4.2 Sonocrystallization:

A novel approach for particle size reduction based on crystallization using ultrasound is known as Sonocrystallization. This technique harnesses ultrasound power within the frequency range of 20-100 kHz to induce crystallization. Sonocrystallization not only enhances the nucleation rate but also serves as an effective means of reducing the size and controlling the size distribution of the active pharmaceutical ingredient (API). This technique is commonly applied using ultrasound in the range of 20 kHz to 5 MHz. Sonocrystallization has also been explored as a method to address the challenges associated with non-steroidal anti-inflammatory drugs (NSAIDs), such as poor solubility, dissolution rate, and consequently, poor bioavailability.

4.3. Melt emulsification method:

Solid lipid nanoparticles are primarily prepared through the melt emulsification method. Kipp and colleagues were among the first to create nanosuspensions of ibuprofen using this approach, which involves a four-step procedure. The drug is initially added to an aqueous solution containing a stabilizer. The solution is then heated to a temperature higher than the melting point of the drug and homogenized using a high-speed homogenizer to form an emulsion. The temperature is maintained above the melting point of the drug throughout the entire process. Finally, the emulsion is cooled to precipitate the particles. The particle size of the nanosuspension is primarily influenced by parameters such as drug concentration, the concentration and type of stabilizers used, cooling temperature, and the homogenization process.

4.4. Bottom-Up NanoCrySP Technology:

G. Shete, Y. Pawar, et al. from the National Institute of Pharmaceutical Education and Research (NIPER) introduced a novel method for generating Nano Crystalline Solid Dispersion (NSD) of hesperetin using NanoCrySP technology. This innovative bottom-up process, based on spray drying, produces solid particles containing drug nanocrystals dispersed in the matrix of small molecule excipients (WO2013132457 A2). The objective of their study was to enhance the oral bioavailability and pharmacodynamics activity of hesperetin nanocrystals generated using this novel bottom-up NanoCrySP Technology.

In their approach, hesperetin and mannitol were used in a 1:1 ratio, and NSD was generated through spray drying. The process of NSD formation is rooted in classical nucleation theory, where mannitol contributes to the crystallization of hesperetin by acting as a plasticizer, crystallization inducer, and by providing heterogeneous

nucleation sites. The results showed that hesperetin existed as nanocrystals dispersed in the matrix of mannitol, with an average crystallite size of 137 nm in the NSD [14**]**.

❖ NANOCRYSTAL STABILIZERS:

The numerous impressive advantages of nanocrystals notwithstanding, the small size of nanocrystals can often give rise to stability concerns. The large surface area of nanocrystals leads to a sufficiently high free energy or surface charge, which may cause attraction or agglomeration [14]. Small-sized nanocrystals can sometimes elevate the solubility of a drug beyond the saturation point, promoting recrystallization into larger particles—a phenomenon known as Ostwald ripening. These processes can ultimately result in the irreversible loss of formulation integrity [15]. To mitigate these challenges, various stabilizers are employed for the stabilization of nanocrystals.

a. Poloxamer

Poloxamers are amphiphilic block copolymers formed through a combination of ethylene oxide (E; hydrophilic) and propylene oxide (P; hydrophobic) units arranged in an E–P–E configuration. These polymers are available in various grades, developed using different lengths of polymer blocks. Poloxamers not only serve as ideal stabilizers but also exhibit the capacity to sensitize multiple drug resistance (MDR) cells. They are certified as generally recognized as safe (GRAS) excipients and are known for causing minimal hemolytic reactions, making them popular for drug delivery via the intravenous route [16].

Poloxamers have found widespread use in the stabilization of nanocrystals. Nanocrystals of omeprazole appended with Poloxamer 188 exhibited enhanced stability, attributed to the shielding effect of the compound. In comparison with an omeprazole solution, the nanocrystals demonstrated improved stability. Researchers have also employed Poloxamer 407 in the development of various nanocrystal formulations. Deng et al. aimed to enhance the therapeutic profile of paclitaxel by stabilizing its nanocrystals using Poloxamer 407; however, they inadvertently ended up with a thermosensitive micellar structure. Subsequent renanonization through incubation and sonication successfully led to the formation of nanocrystals with prolonged stability [17, 18].

b. Polyvinyl Pyrrolidone (PVP)

PVP or povidone is prepared by reaction of acetylene and pyrrolidone to form vinyl pyrrolidone followed by polymerization to convert into PVP. It is available in different viscosity grades having a versatile range of application from being a binder in tablets and capsules, film formers in ophthalmic solution, taste masking agent, toxicity reducer and the most important as a stabilizer in suspensions[19].PVP K30 has been applied as a stabilizer for formation of celecoxib Nanocrystals Remarkably, it was seen that combination of stabilizers did not affect the crystallinity of drug when characterized by DSC; however a reduction of melting point was seen due to generation of new crystalline state.[21] PVP K17 and K12 demonstrated the versatile applications of PVP when they were tried for the preparation of probucol nanocrystals. The study established the fact that PVP or SDS alone was incapable to prevent agglomeration whereas combination of both resulted in a stable formulation.[20]

c. Polyvinyl alcohol (PVA)

The properties of water-soluble polyvinyl alcohol (PVA) depend on the degree of polymerization and the extent of hydrolysis. Partially hydrolyzed PVA is commonly employed in the pharmaceutical industry [22]. It has been utilized in formulating stable nanocrystals of nitrendipine, a class II calcium channel blocker. The formulation was achieved through a precipitation ultrasonication method, leading to improved dissolution characteristics and subsequently increased oral bioavailability of nitrendipine [23].

d. Amino acid derived co-polymers

Albumin, a single polypeptide chain consisting of 585 amino acids, is commonly employed as a stabilizing agent for parenteral formulations containing proteins and enzymes. Leucine (C6H13NO2) has found utility as a lubricant and antiadherent in the development of aqueous nanocrystal formulations. Lee et al. experimented with various copolymers derived from amino acids to stabilize nanocrystals containing naproxen. Nanoformulations were created using two polymeric combinations composed of lysine, leucine, and albumin. However, the use of

albumin is often associated with potential side effects such as anaphylactic hypersensitivity reactions, hyperlipidemia, abnormal lipoprotein patterns, erythrocyte aggregation, and peripheral neuropathy [23, 24].

e. Lecithin Lecithin

Lecithin, a mixture of phosphatides with triglycerides, fatty acids, and carbohydrates, plays a crucial role in many nutritional formulations due to its lipid content. In the pharmaceutical industry, lecithin excels as a stabilizer or emulsifier. Its physical forms may vary from powders to semi-liquids based on their free fatty acid content, and they also possess good absorption-enhancing properties. Derived from natural sources such as eggs and soy, lecithin is widely accepted as a stabilizer for various drugs.

Lecithin has been utilized in combination with Poloxamer 188 and HPMC to stabilize amoitone B, an anticancer agent. Yang et al. employed dipalmitoyl phosphatidylcholine (a form of lecithin and an endogenous component of human lung surfactant) to formulate nebulized itraconazole nanocrystals with improved bioavailability. The presence of dipalmitoyl phosphatidylcholine ultimately enhanced the in-vivo presence of itraconazole due to its permeation enhancement property.

❖ APPLICATION OF NANOCRYSTALS:

1.Oral drug delivery

The oral route is widely preferred and considered the safest and most suitable method for drug delivery [25, 26]. In the case of orally administered drugs, dissolution is often identified as the rate-determining step for absorption. Nanocrystals present a larger surface area for dissolution, thereby increasing the saturation solubility and enhancing the dissolution rate. Muller et al. have advanced the oral delivery of thermally stable drugs by using melted polyethylene glycol (PEG) with a melting point at 60 °C, enabling the fixation of nanocrystals in a solid PEG matrix. Nanocrystals dispersed in melted PEG were milled to powder and directly compressed into tablets or filled into capsule shells. This innovative drug delivery system provides a means to incorporate poorly soluble drugs directly into tablets, capsules, or hot melt solid matrices to improve oral bioavailability [29]

2.Intravenous drug delivery

Administering a drug intravenously provides several advantages, such as rapid action, lower dosing requirements, and 100% bioavailability. However, the utilization of the intravenous route is constrained by the concurrent administration of harmful solvents and excipients used in formulation development, which can lead to severe side effects beyond those associated with the drug itself. Nanocrystals are deemed as ideal candidates for intravenous delivery due to their developmental processes, which do not entail excessive use of such harmful excipients [27].

3 Pulmonary drug

Lungs, as highly perfused organs with a surface area equivalent to three football fields, lack hepatic portal drainage. This results in the rapid and efficient systemic circulation transport of molecularly dispersed drugs. Recent studies have demonstrated that pulmonary nanocrystals can match the pharmacokinetics achieved by intravenous administration of baicalin. Therefore, the pulmonary route emerges as a viable option for therapeutic delivery. Given its constant exposure to the external environment, the respiratory tract is susceptible to disease-causing agents, allergens, and pathogens. Modification of conventional methods for deep lung drug deposition involves tailoring the size of nanocrystals. Nebulizers are typically used to administer powdered nanocrystals, allowing for their incorporation into small inhalable droplets (1–5 μm) [28,29].

4 Ocular drug delivery

Ophthalmic drug delivery presents a significant challenge due to the intricate pharmacokinetic environment and physiological barriers of the eye, hindering effective drug delivery. Traditional formulations, delivered topically as solutions or suspensions, face rapid clearance from the application site due to blinking and lacrimation, resulting in low ocular availability. The short retention time of medication necessitates repeated dosing, impacting patient compliance and leading to dose-dependent side effects. Various approaches, such as ocular inserts and ophthalmic gels, have been explored to address these challenges, but they come with their own drawbacks, including poor therapeutic outcomes, blurred vision, and local irritation.

Colloidal drug delivery systems were initially introduced to improve ophthalmic drug delivery, with Piloplex being a notable example. This system incorporates pilocarpine, ionically bound to poly(methyl) methacrylate-co-acrylic acid nanoparticles. Subsequently, nanocrystals technology has played a pivotal role in overcoming the dispersibility challenges of poorly soluble drugs like budesonide, dexamethasone, hydrocortisone, prednisolone, and fluorometholone.

Researchers, such as Ali et al., have employed a combination of microfluidic nanoprecipitation and wet milling to create nanocrystals of hydrocortisone. The ocular bioavailability of these nanocrystals was evaluated in albino rabbits, demonstrating an extended duration of action and significantly improved AUC compared to free drug. Another notable advancement in ophthalmic delivery involves forskolin, an intraocular pressure-lowering agent. Nanocrystals of forskolin were incorporated into an in-situ gelling system comprised of poloxamer and polycarbophil. Pharmacodynamic studies revealed that the nanocrystals/hydrogel system efficiently lowered intraocular pressure for up to 12 hours compared to conventional suspension formulations.

5.Bioavailability Enhancemen

Nanosuspensions offer a solution to the challenges posed by newly developed molecules with poor water solubility, leading to poor permeability. These formulations address both issues of low solubility and limited permeability across membranes, thereby enhancing bioavailability. For instance, when comparing oral administration of naproxen nanoparticles to conventional naproxen, the area under the curve (AUC) (0-24 h) significantly improves to 97.5 mg-h/l, compared to 44.7 mg-h/l for naproxen suspensions and 32.7 mg-h/l for anaprox tablets.

In the case of the gonadotropin inhibitor Danazol, conventional dispersion (Danocrine) exhibits only 5.2% absolute bioavailability. However, in the form of a Nanosuspension (Danazol), the bioavailability dramatically increases to approximately 82.3%. Another noteworthy example is the Nanosuspension of Amphotericin B developed by Kayser et al., which demonstrated a significant improvement in oral absorption compared to conventional commercial formulations. These instances highlight the substantial enhancement in bioavailability achieved through the utilization of nanosuspensions for poorly water-soluble compounds.[13]

6.Targeted Drug Delivery

Nanosuspensions offer a versatile platform for targeted drug delivery, allowing easy modification of their surface properties and in-vivo behavior by altering the stabilizer or environmental conditions. The development of stealth nanosuspensions, similar to stealth liposomes, involves employing various surface coatings for active or passive targeting of specific sites, representing the future of targeted drug delivery systems.

An example of this targeted approach is demonstrated by Kayser et al., who formulated a nanosuspension of Aphidicolin to enhance drug targeting against leishmania-infected macrophages. The nanosuspension formulation exhibited increased activity with an EC(50) of 0.003 mcg/ml, compared to approximately 0.16 mcg/ml in the conventional form.

Similarly, Scholer et al. showcased improved drug targeting to the brain for the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii. They utilized a nanosuspension formulation of Atovaquone, highlighting the potential of nanosuspensions for targeted drug delivery in diverse therapeutic applications.[13]

❖ MARKETED FORMULATION OF NANOCRYSTALS

1.Rapamune: In the year 2000, Wyeth Pharmaceuticals introduced the first US FDA-approved oral nanocrystals. This innovative product, known as Rapamune, featured Sirolimus nanocrystals incorporated into an excipient mixture designed for direct compression into easily consumable tablets. The oral bioavailability of the nanocrystal tablets demonstrated a remarkable 21% increase compared to the conventional Sirolimus solution. Prior to the availability of Rapamune, Sirolimus was only offered as an oral solution, necessitating refrigeration storage and the need to be mixed with water and orange juice before administration.[29]

2. Emend: In 2001, Merck (Winehouse Station, NJ) introduced Emend, a medication containing Aprepitant, primarily used for the treatment of emesis (nausea and vomiting). Aprepitant acts as a selective, high-affinity antagonist of human substance P/neurokinin 1 (NK 1) receptors. Unlike existing therapies for chemotherapy-induced nausea and vomiting (CINV) that target serotonin (5-HT3), dopamine, and corticosteroid receptors,

Aprepitant demonstrates little or no affinity for these receptors. In animal models, Aprepitant has shown efficacy in inhibiting emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, through central actions. Emend is available in capsule form, containing 80 or 125 mg of Aprepitant formulated as nanocrystals drug particles.[30]

3.Tricor: Tricor, introduced to the market by Abbott Laboratories, features fenofibrate as its active ingredient and is available in tablet form with strengths of 48 mg and 145 mg. Tricor is indicated as adjunctive therapy to diet in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson types IIa and IIb). Its purpose is to increase high-density lipoprotein cholesterol (HDL-C), reduce triglycerides (TG), reduce low-density lipoprotein cholesterol (LDL-C), reduce total cholesterol (Total-C), and reduce Apolipoprotein B (Apo B).[31,32]

4. Megace ES : Megace ES (megestrol acetate) was introduced by Par Pharmaceutical Companies, Inc. (Spring Valley, NY), having licensed the Megace name from Bristol-Myers Squibb (New York). Megestrol, a synthetic progestin, shares physiologic effects with natural progesterone. It exhibits direct cytotoxic effects on breast cancer cells in tissue culture and suppresses luteinizing hormone release from the pituitary. Primarily used to enhance weight gain and appetite in patients undergoing chemotherapy or dealing with an HIV infection, the nanosized drug can be formulated in a smaller volume. The reduced volume, along with improved bioavailability, allows for better patient compliance through flexible dosing, leading to effective appetite stimulation and weight gain with a reduced daily dose of 625 mg of Megestrol in 5 ml of fluid compared to the available oral solution.[33.2]

a nanocrystal technology: to enhance solubility of poorly water soluble drugs

Trade name	**Drug**	**Indication**	**Applied technology**	**Company**	**Status**
Rapamune	Rapamycin	Immunosuppressive	Nanocrystals élan	Wyeth	Marketed
Emend	Aprepitant	Anti emetic	Nanocrystal élan	Merck	Marketed
Tricor	Fenofibrate	Hypercholesterolemia	Nanocrystal élan	Abbott	Marketed
Megace ES	Megestrol	Anti anorexic	Nanocrystal élan	Par Pharmaceutical Companies	Marketed
Triglide	Fenofibrate	Hypercholesterolemia	IDDP Skyepharma	Sciele Pharma Inc.	Marketed
Semapimod	Guanylhydrazone	TNF-α inhibitor	Own	Cytokine Pharmasciences	Phase II
Paxceed®	Paclitaxel	Anti inflammatory	Unknown	Angiotech	Phase III
Theralux®	Thymectacin	Anti cancer	Nanocrystal Élan	Celmed	Phase II
Nucryst®	Silver	Anti bacterial	Own	Nucryst Pharmaceuticals	Phase II

❖ CONCLUSION :

In conclusion, drug nanocrystals represent a crucial formulation approach for poorly water-soluble drugs, effectively addressing challenges related to solubility and bioavailability. This technology is versatile and applicable to a wide range of poorly water-soluble drugs, leading to a significant reduction in particle size within the nanometer range. Solubility enhancement is a key aspect, particularly for drugs with narrow therapeutic windows, ensuring improved bioavailability through increased solubility and dissolution velocity. Nanocrystals offer advantages such as the elimination of problematic surfactants (e.g., Cremophor EL), reducing the risk of side effects or adverse reactions.

The rapid dissolution of nanoparticles enables fast action onset, making it advantageous for drugs that require quick efficacy, such as naproxen for headache relief. Additionally, the modification of nanocrystal surfaces allows for controlled and targeted release, providing flexibility in drug delivery. One notable benefit of drug nanocrystals is the potential for administering smaller doses to achieve moderate blood levels, thereby minimizing side effects associated with larger dosages. This technology is applicable across various administration routes, including oral, parenteral, ocular, pulmonary, and dermal delivery.

Liquid nanosuspensions can serve as liquid dosage forms or be transformed into solid dry powder for the production of tablets, capsules, or pellets. Several techniques, such as granulation fluid preparation for tablet production, layering dispersion in fluidized bed processes, use of solid/liquid PEG, spray drying, and lyophilization, can be employed to solidify nanosuspensions. These techniques contribute to the development of final dosage forms with higher drug loading capacity, improved redispersibility at the site of action, and enhanced drug targeting. Overall, drug nanocrystals offer a promising solution to overcome challenges associated with poorly water-soluble drugs in pharmaceutical formulations.

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