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A REVIEW ON PHARMACEUTICAL NANOCRYSTALS

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Abstract:
About 40% of drugs on the market have problems with poor solubility in water, and it has been found that 70% of the molecules in water are practically insoluble in water. Nanocrystals can be prepared by top-down, bottom-up and combinatorial methods. Many patented products such as Nanocrystals®, DissoCubes®, NANOEDGE® and SmartCrystals® are based on our plans. The reduction in size leads to instability of the nanocrystalline system and Austenitic maturation to occur. Nanosuspension can be converted to a steady state by performing various processes, such as freeze drying, spray drying, pelleting, and pelleting to prevent solid state particles from aggregating. These techniques are known for their scalability and continuous nanocrystal formation. Nanocrystals can be characterized using Scanning Electron Microscopy, Transmissive Electron Microscopy, Atomic Force Microscopy, Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy, Powder X-ray Diffraction, and Photon Correlation Spectroscopy. One of the biggest advantages of nanocrystals is their wide range of applications such as oral administration, ocular administration, pulmonary administration, transdermal administration, intravenous administration and target (brain and tumour target).

KEYWORDS: *Nanocrystals, Ostwald ripening, Bioavailability, Pearl milling, Lyophilisation*

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INTRODUCTION:

The number of newly developed drug molecules displaying poor bioavailability because of low aqueous solubility is steadily increasing. Methods that are used to increase the solubility of poorly soluble drugs, can be categorized as "specific approaches" and "non-specific approaches". . In order to qualify for a specific approach, the drug molecule must possess specific physicochemical properties On the other hand, the “non-specific” approaches are applicable to almost any drug molecule (apart from a few exceptions) to improve its solubility. One of the most successful examples of this non-specific formulation strategy is the micronization of the drug which increases the surface area per unit volume of the drug, resulting in a high dissolution rate and eventually the high concentration of drugs at the absorption/action site. The colloid mills and jet mills are prominently used instruments in industries for the Micronization of the drug. Micronization can reduce the drug particles into the range of 2 to 5 µm, with the size distribution range of approximately 0.1 to 20 µm in many cases; micronization alone cannot produce the required surface area that can increase the dissolution rate of the drug. To address this constraint, researchers have moved one step further i.e. from micronization to Nanonization which is known as drug nanocrystals technology US-FDA considers nanotechnology as an emerging technology that has applicability in broad areas such as medical products (e.g. to increase the bioavailability of a drug), foods (e.g., to improve food packaging) and cosmetics (e.g. to affect the look and feel of cosmetics). US-FDA describes nanomaterial as a material or end product designed to exhibit physical, chemical, or biological properties attributable to its Nano size dimensions (up to 1,000 nm). Materials in the nanoscale range may have different chemical, physical and biological properties such as bioavailability, dose requirement, potency, toxicity, and ability to detect pathogens com-pared to their micro/coarse size counterparts.Drug nanocrystals are defined as pure solid drug particles with a mean diameter below 1000 nm. They are composed of repeated lattices of atoms, ions, or molecules. Increased rate of absorption,

• Increased oral bioavailability,
• Rapid effect,
• Improved dose proportionality

This kind of specific arrangement is usually achieved by either direct crystallization (bottom-up approach) or milling (top-down approach) of bulk material. Drug nanocrystals are pure active pharmaceutical ingredient (API) stabilized by appropriate excipients. Another related term is drug nanosuspension which is a dispersion of drug nanocrystals in a suitable medium, stabilized by using appropriate excipient such as surfactants and/or long-chain polymers. The dispersion medium can be water, other aqueous solutions, or non-aqueous liquid. It should be noted here that the word "drug nanocrystals" does not only mean crystalline discrete particles but can also be partially or completely amorphous material depending on the methods of production. Strictly speaking, if the drug is in amorphous form then the word "crystals" cannot be used to describe it but many publications in which drug molecules were confirmed to be in the partial crystalline state have used the term "Nano crystals" to describe it. Recently, preparations having drug molecules in other than pure crystalline form have used terminology such as “amorphous nanoparticles” or “amorphous drug nanosuspension” to describe it[1, 2].

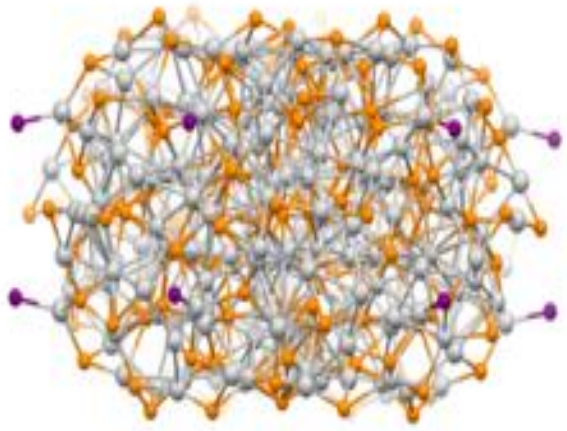

Fig 1: Nanocrystals

ADVANTAGES OF DRUG NANOCRYSTALS

- Universal method to increase solubility of poorly soluble drugs.
- No use of surfactant.
- Produces a drug powder which can be incorporated into a variety of dosage forms.
- Stable
- Cost effective process.
- Uses generally regarded as safe (GRAS) materials.

DISADVANTAGES OF DRUG NANOCRYSTALS[3]

- Limited drug loading capacity.
- Slowly biodegradable which might cause toxicity.
- On repeated administration, toxic metabolites may be formed.

NANOCRYSTAL TECHNOLOGY[4, 5]

Drug Nano crystals can be prepared by a bottom-up method (precipitation method) or a top-down method (size reduction by milling or high pressure homogenization). In the case of bottom-up techniques, it starts with molecules in solution and proceeds through the combination of these molecules to form solid particles. That is, it is a classical precipitation process. The top-down method is based on reducing the size of relatively large particles to smaller ones by mechanical attrition. For industrial production, all products are prepared according to top-down technology. Here are the main methods currently used by various companies:

- Bottom-up technique (Precipitation method)
- Top down techniques
- Pearl/Ball milling (Nano systems /Élan technology)
- High Pressure Homogenization (HPH)
- Micro fluidizer technology (IDD-PTM technology)
- Piston gap homogenization in water (Disso cubes® technology)
- Piston gap homogenization in water mixtures or in non-aqueous medium (Nano pure® technology)
- Combination technology
- NANOEDGE Technology
- Smart Crystal Technology

Bottom-up technology (Precipitation method)[6]

This is also known as hydrosol technology. This was developed by Sucker and the intellectual property is owned by Sandoz. . In this method, after dissolving a drug in a solvent, the solution is added to a non-solvent to precipitate fine drug nanocrystals. The deposition method is simple and requires inexpensive equipment. For example, the solvent can be poured into a precipitator at a constant rate with a high-speed stirrer. The main approaches include static mixers or micromixers (i.e., laboratory conditions simulated). In the case of micromixers, scaling can be accomplished in a simple manner by placing several micromixers in parallel. This equipment is relatively simple and relatively inexpensive (not necessarily applicable to micromixers).

A disadvantage of this method is that the drug must be dissolved in at least one solvent. However, this is a problem for newly developed drugs that are generally insoluble in both aqueous and organic media. Second, this solvent must be miscible with at least one non-solvent. Solvent residues must be removed, which increases production costs.

In the case of nanocrystals, care must be taken to ensure that the crystals do not increase in size and remain stable at the nanoscale. Spray drying and lyophilization are recommended methods to keep the particle size in the nano range. Another alternative to maintaining nanocrystal size is to use polymer growth inhibitors. Various stabilizers such as sodium dodecyl sulphate (SDS), polyvinyl alcohol (PVA), tween 80 and polyxamer 188 have been used to fabricate the nanocrystals.

Nanomorphs: Soliqs/Abbott has developed another precipitation method to improve dissolution rate and solubility. Carotene nanoparticles have been developed for the food industry, such as Leucarotin or Lucantin (BASF). To prepare it, a solution of carotenoids and surfactants in digestible oil was mixed with an appropriate aqueous solvent. A protective colloid is added to it. Carotenoids were stabilized and localized in the oil phase of this O/W emulsion. This emulsion was then lyophilized. X-ray diffraction analysis of the lyophilized product showed that about 90% of the carotenoids were in the amorphous state. These particles are called Nanomorph. They are found to have higher saturated solubility compared to crystalline materials. There are currently no drugs on the market based on this technology[7].

Top-down techniques

1. Pearl/Ball milling

In this method, the drug is fed into the grinding chamber along with a grinding medium, a dispersion medium (usually water) and a stabilizer. Grinding balls or small pearls are used as the grinding medium. . The motion of the grinding media creates high shear and impact forces to reduce particle size. This technology was developed by Merisko-Liversidge et al. (2003). Pearls or beads are composed of ceramic (cerium or yttrium stabilized zirconia), glass, coated stainless steel beads or highly cross-linked polystyrene resins. Two basic milling principles are used. The material to be ground can be moved to the agitator or the entire vessel can be moved in a complex motion. Agitation mills are generally preferred for large batches as the latter method is difficult to handle large batches. However, grinding time depends on various factors such as drug hardness, surfactant content, viscosity, temperature, energy input, and grinding media size. Grinding times can last from 30 minutes to several hours.

The advantages of pearl grinding are low cost, simple technology and the possibility of large-scale production. Disadvantages associated with this process are contamination of the product due to erosion of the material to be ground, sticking of the product to the inner surface of the mill and the surface of the milled granules, and long grinding

times (for hard drugs).), potential microbial growth in the aqueous phase (during long milling), and the time and cost associated with the procedure for separating the milled material from the suspension of drug nanoparticles, especially when obtaining a parenterally sterile formulation.

2. High Pressure Homogenization Technique

This technology has been used for the production of emulsions and suspensions for many years. A distinct advantage of this technology is its ease of scalability. There are three important techniques for producing nanocrystals using the homogenization method[8].

- Micro fluidizer technology (IDD-PTM technology).
- Piston gap homogenization in water (Disso cubes® technology).
- Piston gap homogenization in water mixtures or in non-aqueous medium (Nano pure® technology)

Microfludizer Technology

This technology is based on the principle of jet flow. Two fluid streams at high speed (up to 1000 m/s) collide head-on at high pressure (up to 1700 bar). Particle size decreases due to high shear particle collisions and cavitation25. The same can be achieved using a jet stream homogenizer such as the micro fluidizer. The impact chamber can be Y-shaped or Z-shaped. A surfactant or phospholipid is required to stabilize the desired particle size.

Microfluidization devices can be used to produce nanosuspensions for soft drugs. However, this method is not suitable for large-scale production because it requires a large number of cycles (50 to 100 passes) to sufficiently reduce particle size. This method is used by SkyePharma Canada Inc. For the production of submicron particles of poorly soluble drugs, it is called IDD-PTM (Insoluble Particle Technology for Drug Delivery).

Piston gap homogenization in water

(Disso cubes® technology). The piston gap homogenization technology was developed by Müller et al. and acquired by SkyePharma in 1999. In this method, a powdered drug is dispersed in an aqueous surfactant solution and then pushed by a piston through a small high-pressure homogenizing gap. The gap width is adjustable depending on the viscosity of the slurry and the applied pressure, and typically ranges in size from 5 to 20 μm. According to Bernoulli's equation, the resulting high slurry flow rate increases the dynamic pressure, which is offset by a decrease in static pressure. The static pressure in the gap falls below the vapour pressure of water at room temperature. Thus, water will begin to boil in the gap at room temperature, and bubbles will form. The formation of air bubbles creates pressure waves that destroy the crystals. As the liquid exits the homogenization slot, the static pressure increases to normal pressure and the bubbles collapse. This process of formation and collapse of bubbles is called cavitation. Particle size decreases due to the high shear forces, turbulence and the enormous force of these shock waves. This method was used to produce nanosuspensions of artemisinin and quercetin using Tween 80 as a stabilizer (0.5–2.5% w/w). The use of water as a dispersion medium has several disadvantages, such as hydrolysis of water-sensitive drugs and problems in the drying step. For heat-labile drugs or drugs with low melting points, methods such as lyophilization are required to remove water, which is costly. Dissocubes® technology is therefore best suited when aqueous suspensions of nanocrystals for drugs that are poorly soluble in both aqueous and organic media must be prepared.

Piston-gap homogenization in water reduced mixtures or non-aqueous medium

Another approach using a piston gap homogenizer is the Nanopure® technology owned and developed by Pharmasol GmbH in Berlin. In this technique, a non-aqueous phase or a phase with reduced water content is used as the dispersion medium. Using a non-aqueous medium is advantageous for drugs that hydrolyse in water. Various media used for homogenization include oils, water-glycerol mixtures, polyethylene glycols, water-alcohol mixtures, etc. These dispersion media have low vapour pressure. The static pressure in the homogenizing gap does not fall below the vapour pressure of the liquid, so the liquid does not boil and cavitation does not occur. Sufficient size reduction down to the nanoscale is possible without cavitation. The forces responsible for the size reduction are particle collision forces and shear forces generated in highly turbulent fluids in the interstitial space. Nanopure® homogenizers are equally or more effective at lower temperatures, i.e. below the freezing point of water. A molten non-aqueous matrix such as PEG 6000, which is a solid at room temperature, can also be used as a homogenization medium. This immobilizes the drug nanocrystals in the solid matrix and minimizes crystal contact and subsequent crystal growth[9].

Nanocrystals are used in powder form for the production of solid dosage forms such as tablets and pellets. Preparation of solid oral dosage forms from nanocrystals suspensions requires removal of the dispersion medium from the nanocrystals. The

dispersion medium is removed by lyophilisation or spray drying. The advantage of Nano pure technology in this case is that evaporation occurs faster and at lower temperature due to the use of non-aqueous media or mixtures with reduced water content. This is useful for heat labile drugs.

Combination Technologies

The term combination technology has been used for technologies which combine a pre-treatment step followed by a high energy homogenization.

- **NANOEDGE Technology**

This technology was introduced by Baxter, and this involves a combination of precipitation followed by annealing process. Annealing process is carried out using high energy such as high shear forces and/or thermal energy. When drug nanoparticles are produced by precipitation method alone, the precipitated nanoparticles have a tendency to grow. Also, the precipitated particles may be amorphous. Upon keeping, the amorphous particles may recrystallise and this may lead to a decreased bioavailability of the drug. Combination technology on the other hand has the potential to overcome these problems, firstly, by prevention of crystal growth and secondly by reducing the uncertainty of formation of either crystalline or amorphous state as the annealing process convert all precipitated particles to crystalline state. TM Nano edge technology is particularly suited for water-insoluble drugs with low toxicity, such as N-methyl-2-pyrrolidinone. A disadvantage of this method is cost, especially in the manufacture of sterile parenteral preparations.

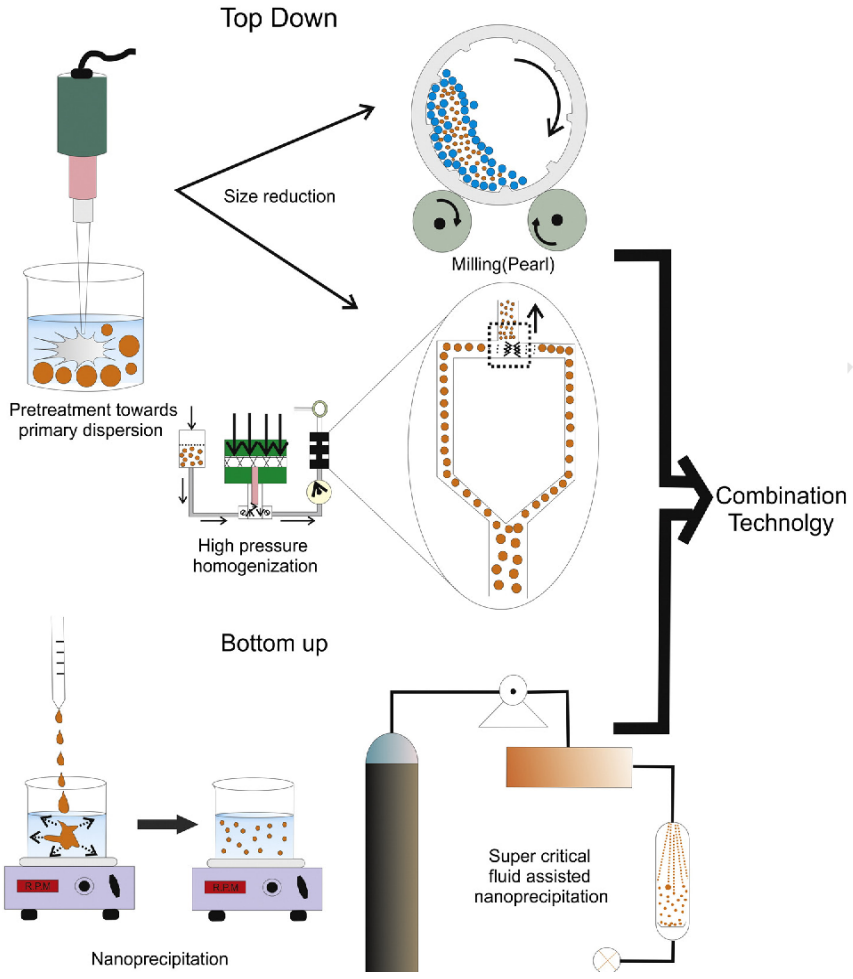

Fig 2: Nanocrystal Technology

STABILITY OF NANOCRYSTALS[10, 11]

Drug Nano crystallisation leads to the reduction in particle size, increase in surface area, and increase in Gibbs free energy of the system which leads to thermodynamically unstable nanosuspensions the particles will tend to lose energy to get stabilize and forms agglomerates. This phenomenon is called Ostwald ripening which affects the long term stability of nanosuspensions. However, the stability depends on the nature of stabilizers and their concentration used. Kinetic stability of the nanosuspensions controlled by an activation energy of the system and surface forces such as hydrophobic forces which plays an important role in agglomeration. The factors affecting the stability of the nanosuspensions include physiochemical properties of the drug, surface energy, wettability, surface hydrophobicity and affinity of the stabilizer towards the particle surface of the drug molecule. For amorphous or partially amorphous nanocrystals, the risk of recrystallization increases, which can eventually lead to Ostwald maturation and instability.

Ostwald ripening in highly dispersed systems is due to the disappearance of the smallest particles and the formation of micro particles. Difference in saturation solubility due to different particle sizes results in the existence of a concentration gradient that causes smaller particles to diffuse into the environment of larger particles. This creates supersaturation and crystallization on the larger surface of the particles causes microparticles to form ad smaller ones to disappear. Therefore, the size uniformity as well as the stabilizing layer surrounding the nanocrystals plays an important role in stabilizing the nanosuspensions. Stabilizers adsorbed on the particle surface reduce the free energy of the system as well as the interfacial tension, making the nanoemulsion electrostatistically and sterically stable. The marketed nanocrystals product of drug aprepitant has a shelf life of 4 years[12].

PROCESSING OF NANOSUSPENSION TO FORM NANOCRYSTALS[13]

The nanonionization of drugs by various techniques generally results in a liquid product called nanosuspension. But these nanosuspensions are directly used as a final product only in some special cases e.g. as paediatric or geriatric dosage forms. In most of the cases, a dry dosage form (particularly for oral administration) is preferred, may be

a) For convenience,
b) To achieve a controlled drug delivery,
c) To prevent drug degradation,
d) To enable better drug targeting,
e) To increase the physical stability for long term storage
f) To obtain a fine non-aggregated suspension in the gastro-intestinal tract after oral administration.

In these cases, the nanosuspension must be converted to a solid form that can be crystalline (nanocrystals) or amorphous (nanomorphs). For this, various methods are used, such as spray drying, granulation or granulation.

Spray drying: Spray drying is suitable for industrial production as it is a simple and inexpensive method. This method uses a water-soluble matrix material e.g. Polymers (PVP, long-chain PEG or polyvinyl alcohol), sugars (sucrose, lactose) or sugar alcohols such as mannitol and sorbitol. In the next step, the aqueous drug nanosuspension can be spray dried under suitable conditions. The resulting dry powder consists of drug nanocrystals embedded in an aqueous matrix. The loading capacity of the solid powder with drug nanocrystals can be controlled by varying the concentration of the surfactant in the initial aqueous nanosuspension. The advantage of this method is that the drug nanocrystals remain immobilized in the matrix. Avoidance of physical contact minimizes the potential for long-term physical instability such as agglutination and Ostwald maturation. Exceeding a certain maximum loading capacity of the matrix by drug nanocrystals increases the negative impact on crystal growth and separation of micro dispersed forms.

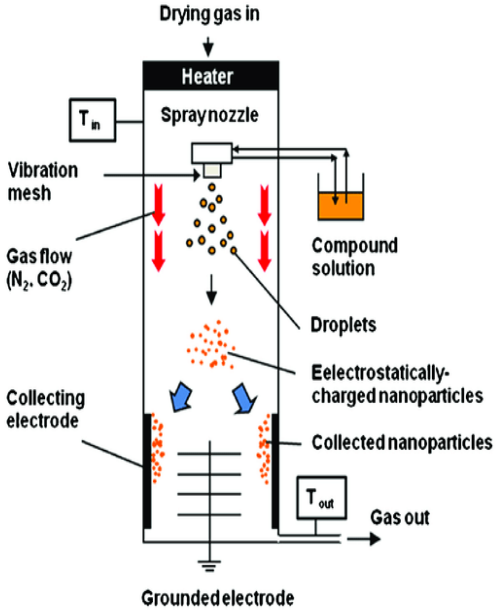

Fig 3: Spray drying

Freeze-drying: Another way to remove water from a formulation is freeze-drying. However, this is a complex and expensive process and the resulting product is very sensitive to process parameters. This method is not suitable for industrial production.

De Waard (2010) developed a new method based on lyophilization. In this method, a mixture of drug, solvent and mannitol is rapidly cooled to isolate the drug in the form of nanocrystals embedded in a matrix of mannitol. This matrix enhances the stability of the nanocrystallized drug, otherwise the crystals can stick together to form one large crystal. De Waard also developed a spray freeze drying method that made the process applicable on an industrial scale. Another method developed by the same authors was the spray freeze drying method which could simplify the industrial application of this process[14].

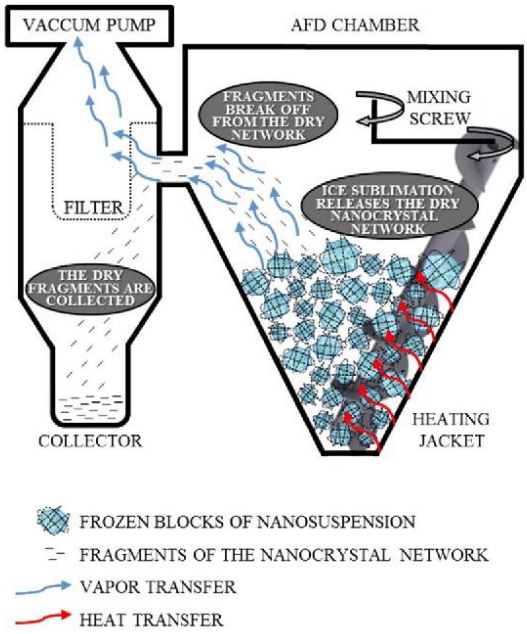

Fig 4: Freeze Drying

Pelletization: A number of Pelletization techniques are known, but the most commonly used techniques are a) extrusion - spheronization and b) drug coating onto sugar spheres. The pelletization technique is selected on the basis of the required drug content, properties of the drug and the available equipment. A multi-particulate dosage form such as coated pellet system is obtained irrespective of the pelletization technique applied. These multi-particulate dosage forms show distinct advantages over single unit dosage forms such as faster and more predictable gastric emptying and more uniform drug distribution in GIT within different individuals.

Production of granules with matrix cores containing drug nanocrystals: The drug nanosuspension obtained by high-pressure homogenization is mixed with a matrix material (filler such as MCC, lactose or star). The pellets are produced by extrusion-spheronization and can subsequently be coated with polymers to modify drug release properties.

Mucoadhesive budesonide nanocrystals were obtained by extrusion-spheronization. The obtained granules were coated with Eudragit L 30 D-55 to obtain an enteric coating and sustained release of the drug. An effervescent pellet formulation containing nanocrystals of the drug ibuprofen is manufactured by HPH. Ibuprofen-containing granules containing drug nanocrystals were completely dissolved within 30 minutes in both formulations.

Spray-coated hydrocortisone acetate granules were prepared (enteric coated) from a Mucoadhesive nanosuspension of this sparingly soluble drug. In vitro dissolution tests showed accelerated dissolution rates and increased drug release for beads comprising drug nanocrystals. The same equipment that changes drug release characteristics.

SOLID STATE CONVERSION OF NANOSUSPENSION AND SCALE METHODS

A variety of single operations such as freeze drying, spray drying, granulation and tableting can be used to convert the nanosuspension into solid form. Scalable and continuous formation of nanocrystals is made possible by using wet milling and agitation with spray drying as well as the approaches described above. In this method, a solvent in an organic solvent is added to an anti-solvent to spontaneously precipitate to form a 10-slurry, which is then immediately dried to form a powder. This robust transformation helps minimize the effects of Ostwald maturation. Stabilizers, as well as cryoprotectants (lactose/mannitol) are added to the antisolvent solution to reduce particle growth and aggregation, keeping the drug as a single unit within the powder. This method has succeeded in achieving continuous production of nanocrystals on an industrial scale. Spray drying is not suitable for heat labile drugs because the process uses high temperatures, whereas freeze drying is the preferred method for these pieces. The particle size of nanocrystals after lyophilization was studied with and without cryoprotectant, which showed that the average size of nanocrystals without cryoprotectant was larger than in the system with cryoprotectant[15].

SCALE DOWN OF NANOCRYSTALS

Reducing the composition of nanocrystals is necessary for screening studies on the composition of nanosuspensions in parallel designs, which have proven to be useful tools in the preclinical stages of drug development because of the very low availability of compounds in the early stages of drug development. Currently, the Avetin EmulsiFlex-B3 is a high-pressure homogenizer that operates with a volume of 3.5 ml. However, for the Media Grinding process, the Nanomill system is designed to operate in the smallest toxicity chamber with a minimum volume of 10 ml. This capacity is also useless when many batches of Clas formulations need to be produced and compound stocks are lower. HPH also forces the slurry through small gaps to reduce the shrinkage potential of this technology, and also achieves grinding media by mixing the toxics made up of the grinding media. In addition, grinding media to produce nanosuspensions is characterized by ease of scaling, which makes the results obtained from nanosuspensions of reduced design valuable. The first references describing media trituration at the microgram level were performed in 24 or 48 well plates, with a minimum amount of 0.5 g[16].

CHARACTERIZATION AND EVALUATION OF NANOCRYSTALS

Nanocrystals can be characterized by particle size, particle size distribution, zeta potential, morphology and solid state behaviour. The stability, in vitro and in vivo performance of the prepared nanocrystals can be evaluated by performing storage stability tests, in vitro drug release studies, and in vivo animal studies.

Particles Size, Size Distribution and Zeta Potential[17]

Photon correlation spectroscopy (PCS) is the most commonly used technique based on the principle of dynamic light scattering to assess the average particle size of nanocrystals in terms of z-value, the particle size distribution and zeta potential (the charge density at the surface of the nanocrystals). PDI values range from 0 (monodisperse particles) to 0.500 (polydisperse particles), which monitor the physical stability of the nanoformulations. Lower PDI values (<0.3) for nanoformulations represent longer stability compared to high PDI formulations. PCS shows incompatibility with larger particle size formulations due to its narrow measurement range of 3 nm to 3µm. in this case, the particle size measurement turned to laser diffractometers (LDs), which can measure particles in a wider range (0.02 to 2000µm), depending on the type of measurement used. Particle size data measured by PCS and LD are not similar because LD data is based on volume distributions, while PCS data represents light intensity-weighted sizes. LD only shows the particle size distribution, while PCS can also measure average particle size and zeta potential, and can also convert intensity data to volume distribution and numerical distribution.

For nanosuspensions intended for intravenous administration, the Coulter counter technique is required to measure the particle size. This technique gives the absolute number of particles per volume for different size classes so that the number of particles in the nanosuspension can be tightly controlled. If particles larger than 5 µm are present in the IV formulation, there is still a risk of capillary clogging because the smallest capillary is 5 µm in size.

Other instruments that can be used to measure particle size distribution are the Scanning Mobility Particle Sizer (SMPS) and the Electric Low Pressure Impactor (ELPI). These instruments are best used to measure the particle size distribution of aerosols. The SMPS is a differential mobility spectrometer whose operation is based on the mobility of particles. The ELPI is a cascade impactor based on charging particles using a monopolar corona charger and then passing the sample through a series of stages in a low voltage cascade impactor consisting of electrically insulating collection stages b. The particles strike at specific stages and generate an electric current, which is recorded by an electrometer. ELPI classifies particles according to their aerodynamic diameter. Particle size measurement using the ELPI is done in near real time.

Shape and Morphology

The size and shape of nanocrystals can be assessed using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis. SEM produces images of the electron beam interacting with atoms at different locations in the sample. Backscattered electrons reflected from a sample by elastic scattering. In TEM, however, the image is the result of the capture of transmitted electrons from the sample. TEM analysis requires wet samples with sufficient particle concentration, while SEM behaviour can image solid dry samples. After lyophilization of the reconstituted nanosuspension, SEM imaging provides information on lithology testing, particle shape, and surface morphology. Atomic force microscopy (AFM) is another very important tool for visualizing nanocrystals, providing qualitative and quantitative information about their physical properties such as size, surface texture, roughness and morphology. Compared with SEM and TEM, it has many advantages because electron microscope can only provide 2D images, while 3D

images of nanocrystals surface can be captured by AFM with is light without any special sample treatment. Copper plating or charring of a sample can cause permanent and irreversible damage to the sample, which is unacceptable when sample recovery is required (in the case of very small sample volumes) .Quantitative information about individual particles as well as between groups of particles, can be generated using AFM. For individual particles, dimensional information such as length, width and height as well as other physical properties such as texture and morphology can be measured. For a set of particles, the required information includes particle number, PDI, volume distribution, and area distribution, which can be obtained by AFM through image analysis and data processing in the software. Particles with a size between 1nm and 5µm can be determined in a single scan using AFM particles[18].

Solid-state characterization

The Enables solid-state characterization of nanocrystals using differential scanning calorimetry (DSC), powder X-ray diffraction (P-XRD), and infrared spectroscopy Fourier transform (FTIR). DSC is a thermal analysis technique that measures thermodynamic changes in a system as a function of heat flow and temperature. Depending on the energy loss or gain, various endothermic and exothermic peaks will be generated. The melting point of the nanocrystals can be determined, which will be observed in the graph as a sharp endothermic peak. Endothermic peaks represent energy expenditure. The amorphous part does not exhibit a distinct melting point, but rather a glass transition temperature. Nanocrystals with smaller particle sizes are close to amorphous and therefore exhibit sharper melting peaks with less intensity than ordinary drug crystals. P-XRD is another tool for evaluating the crystallinity of nanocrystals. The X-ray diffraction pattern of the nanocrystals will also show sharp peaks with reduced intensity or in some cases no peak due to partial or complete amorphization of the drug in the nanocrystals due to homogenization. Molecular-level interactions between drugs and excipients in nanocrystals formulations can be studied using FTIR. FTIR determines interactions based on changes in molecular vibrational frequencies when an interaction occurs between two components.

Storage Stability

Stability evaluation of nanocrystals prepared by can be performed under different storage conditions such as 4°C (refrigerator), 25°C and 40°C in a stability chamber for a specific period of time. The effect of various formulation factors, such as the effect of the type of wetting agent used and the physical state of the nanocrystals (solid or liquid) on the stability of the nanocrystals is typically studied. The stability of the nanocrystals will be evaluated by the size, the polydispersity index (PDI) and the zeta potential of the nanocrystals. The increase in particle size will be caused by particle agglomeration due to Ostwald ripening phenomenon.

In Vitro Drug Release Studies

In vitro drug release studies are performed to assess the rate of drug release from drug nanocrystals. The choice of dissolution medium will be based on the solubility of the drug in the medium or an official pharmacopoeial standard dissolution medium may be used. The particle size of the nanocrystals monitors the overall dissolution rate. Smaller particles provide a higher dissolution rate compared to larger particles due to the higher dissolution rate nanocrystals offer a higher surface area to volume ratio. The dissolution rate of nanocrystals can be controlled by coating the surface with hydrophobic polymers that help maintain drug release.

In vivo studies of nanocrystals[19]

Many research groups have studied the in vivo properties of nanocrystals by administering them to rats or mice by different routes of administration. The in vivo performance of rebamipide nanochips was studied. They observed 1 to 1.57 times higher C_{max} and AUC_{0-24} hours for rebamipide nanocrystals than commercially available formulations, suggesting significantly improved bioavailability of the drug in nanocrystalline form. Similarly, improved the survey bioavailability of baicalein nanocrystals by oral and pulmonary routes of administration. The relative bioavailability of orally administered baicalein nanocrystals was found to be 1.67 times higher than that of orally administered baicalein crystals. Baicalein nanocrystals administered via the pulmonary route also showed rapid and extensive absorption and were noted to have almost the same pharmacokinetic parameters as baicalein administered intravenously.

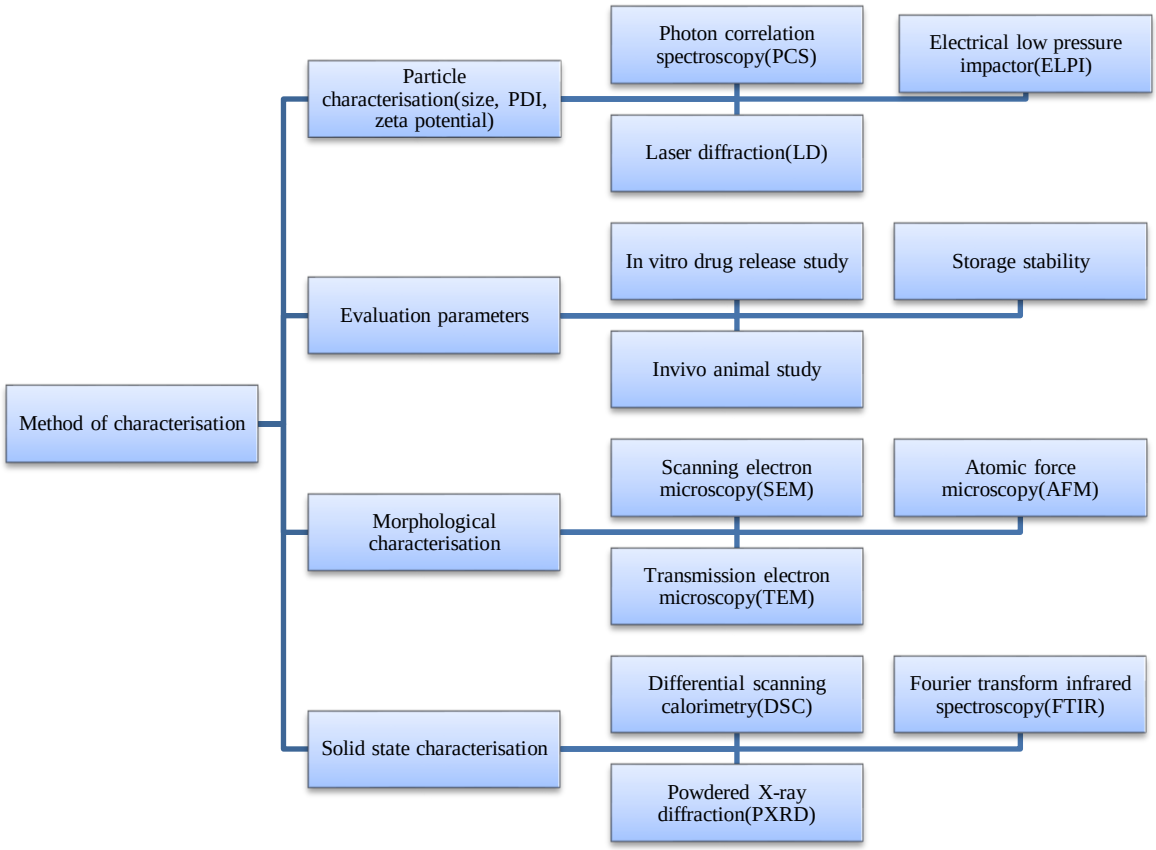

Figure 5: Characterisation methods

APPLICATIONS OF NANOCRYSTALS[20, 21]

Oral Administration

The increased bioavailability of sparingly soluble drugs after oral administration is well documented in the literature. Moreover, there are several drug nanocrystals products on the market to prove this point. Faster onset, less stomach irritation has been reported when naproxen is formulated as a nanosuspension. Drug solubility is enhanced due to the rapid dissolution of nanocrystals, making them bioequivalent under fed and fasted conditions. The bio adhesive properties of nanocrystals provide the added benefit of increased residence in the gastrointestinal tract, which increases bioavailability. The nanoscale size could be used for better drug targeting, as shown for lymphatic drug uptake or inflamed tissue. Nanosuspensions have proven to be very beneficial for oral administration and effectively overcome limiting factors leading to poor bioavailability. When the nanosuspension is administered orally, it provides a higher concentration gradient in the gastrointestinal tract due to increased saturation solubility and dissolution rate. This increases the rate and extent of drug absorption, resulting in high bioavailability.

Parenteral Administration

Intravenous drug administration is required in special cases to meet certain therapeutic goals, such as drugs with rapid onset of action, targeted effects, and first-pass metabolism in the gastrointestinal tract. The drugs achieve 100% bioavailability through the IV route, which cannot be achieved by any other route. For formulations intended for parenteral administration, it should be sterile and particles smaller than 5 µm should not cause toxic or allergic reactions in the body to avoid blockage of smaller capillaries. Parenteral administration of drugs in the form of nanosuspensions is very safe and effective. Nanosuspensions consist of a small amount of stabilizer and 100% pure drug, so they can reduce stabilizer or surfactant (some toxic surfactants) induced and dose-dependent toxicity by reducing injection volume and increasing tolerated dose.

Occular Delivery[22]

Ocular delivery of poorly water-soluble drugs is primarily affected by the inherently limited solubility of the drug in tear fluid, such that low drug levels at the site of action may be achieved. However, when

these drugs are delivered as nanocrystals, the enhanced saturation solubility appears to be beneficial for ocular delivery. Additionally, the nanocrystals have viscous properties that reduce drug loss through tear flow, demonstrating activity for sustained drug release. Researchers investigated drug-loaded polymeric nanosuspensions for the purpose of sustained drug delivery to the eye.

Pulmonary Delivery

Very poorly water-soluble drug particles administered as an aerosol for pulmonary administration are associated with certain disadvantages such as deposition in the mouth and pharynx and clearance of the drug through the cilia of the pulmonary ducts, which are the main cause of drug wastage. The low saturation solubility of poorly water-soluble drugs leads to poor absorption and therefore reduced bioavailability. All of these issues can be resolved when the drug is delivered through the lungs as a nanosuspension. The higher dissolution rate and saturation solubility help the drug quickly reach a high concentration at the site of absorption. The nanosuspension also remained attached to the mucosal layer, preventing drug loss through ciliary movement from the lung ducts. The nanosuspension not only increased the absorption rate of the drug, but also did not exhibit microparticles deposition in the airways, which is common with microparticles[23].

Dermal Delivery

Oral administration of nanocrystals of weakly active substances has attracted more attention and received wide attention in the market. A second area of concern is the intravenous administration of nanocrystals to reduce side effects. However, dermal delivery of nanocrystals to enhance drug penetration and efficacy has long been a neglected area. Today, dermal release is also studied, such as the antioxidant hesperidin; nanocrystalline hesperidin was formed using four different stabilizers, such as Poloxamer 188, inutec SP1, tween 80, and planta care 2000. Tween was found to be less effective in maintaining nanocrystals size.

Targeted Drug Delivery

Due to the control of particle size and surface properties, nanocrystals can be profoundly overdosed to the human body. They can therefore also be used for targeted drug delivery. Nanoparticles offer a promising new cancer treatment that could one day replace radiotherapy and chemotherapy. Kangius RF therapy attaches tiny nanoparticles to cancer cells, and then bakes the tumour into the body with radio waves that only heat the nanoparticles and adjacent cancer cells. Mucoadhesive particles or nanoparticles have been used as specific delivery systems for oral administration.

LIMITATION OF DRUG NANOCRYSTAL TECHNOLOGY[24]

A number of nanoparticle delivery systems are the subject of academic research. But only a few have made it to market. This may be due to lack of nanotoxicity and cytotoxicity data, lack of regulatory approval status of excipients, lack of large-scale production lines validated and accepted by regulatory agencies. The nanotoxicity can be attributed to the small size of the nanocrystals (less than about 150 nm), which allows them to enter any cell in the body through pinocytosis. This increases the risk of cytotoxicity.

In addition, this technique requires expensive equipment, which increases the cost of the final product. The use of this technique is limited to BCS Class II drugs. Moreover, the generation of nanocrystals and their stability depend on the molecular structure of the drug. Therefore, only certain classes of drugs are suitable for this technique.

FUTURE ASPECTS

The drug nanocrystals approach can be applied to various poorly water-soluble drugs to address solubility and bioavailability issues. Along with enhanced bioavailability, drug nanocrystals also exhibit sustained release properties and specific targeting of tissues or organs in some cases. Additionally, drug nanocrystals can be delivered through various routes, such as oral, intravenous, dermal, pulmonary, and ocular. Moreover, the nanocrystals can be transformed into conventional dosage forms (tablets, capsules, injectable aerosols, etc.) if necessary. Nanocrystals can be produced on a large scale using a high pressure homogenization method. The rise in the market value of nanocrystals and the increasing number of commercialized products has attracted attention as a promising method that can be used to achieve commercial benefits. In the future, the effects of nanocrystals at the cellular level should be further investigated to better understand nanocrystals-induced cytotoxicity, intracellular internalization of nanocrystals, mechanisms of internalization[25].

CONCLUSION:

Nanocrystal technology appears to be a promising tool for formulating poorly soluble drugs. Nanocrystals, despite their low solubility, only dissolve and disappear in the presence of large amounts of water. They have been used successfully

to increase bioavailability, better drug targeting and minimal side effects, reduce drug dosage and thus improve patient compliance. They can be incorporated into solid dosage forms such as more patient-friendly tablets and capsules. However, their nanotoxicity needs to be evaluated and more validated therapeutic data wait.

However, nanocrystals are expected to appear in many future products, not only pharmaceuticals but also cosmetics. They can be seen as a beacon of hope for targeted cancer therapy.

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