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OVERVIEW OF NANOCRYSTALS

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ABSTRACT

Nanotechnology is an exciting new area in science, with many possible applications in medicine. This article seeks to outline the role of different areas such as diagnosis of diseases, drug delivery, imaging, and so on Nanocrystals (NCs) are a class of solid dosage forms that take advantage of the drug's crystal structure and the nanoscience idea to improve solubility, dissolution, and physicochemical qualities. When compared to other solid dosage forms, NC frequently faces numerous difficulties with regard to physical stability and chemical stability during the storage and the production process. Thus, crucial steps in the development of NCs include consideration of the physicochemical characteristics of nanocrystals, their hazardous effects on humans, and their use in drug delivery via various routes of administration. To guarantee solid state homogeneity in the NCs and its effect on treatment effectiveness, a number of procedures are used.

KEY WORDS: Nanotechnology, nanocrystals, nanomedicine, development, production process.

INTRODUCTION :

The poor solubility is currently the most significant problem in drug discovery and development. Numerous novel chemical entities demonstrate important therapeutic benefits and increased efficacy, but their limited practical applicability is caused by their poor water solubility. These novel chemical entities fall under BCS classes II or IV in the biopharmaceutics classification system (BCS).[1]As a result, numerous strategies have been developed to address the issue of low aqueous solubility. These methods include salt production, cosolvent, solid state manipulation, emulsions, surface active agents, and micronization.[2,3]The traditional method of medication formulation is known as micronization, which involves reducing the size of drug

powders to a typical range of 1 to 10 micrometres. They frequently are unable to address the bioavailability issue, though. The logical next step after micronization was nanonization.A logical progression is "nanonization," or the reduction of micronized particles to nanoparticles. Many different nanonization techniques have been developed to improve the bioavailability and solubility rates of numerous medications that are poorly soluble in water. These techniques include boosting surface area, altering crystalline morphologies, and creating brand-new nanomaterials that can serve as controlled release carriers.[3,4]Drug nanocrystals are an innovative and adaptable method for enhancing the solubility and bioavailability of pharmaceuticals that aren't very soluble. Drug particle surfaces that have been modified (by increasing surface area) using a nanocrystal method have better adhesiveness. This pioneering nanocrystal technology can be combined with the conventional dosage forms to further add an advantage to the drug therapy.[5]

DEFINITION:[6]

Nanocrystals are surface-stabilized crystalline nanoparticles with sizes ranging from 200 to 500 nm. They improve the oral bioavailability of medicines displaying dissolution rate dependent bioavailability by increasing the saturation solubility, dissolution rate, and perhaps mucoadhesion.

ADVANTAGES OF NANOCRYSTALS :[7,8]

- Any administration channel is acceptable for giving it.
- Increased bioavailability and solubility of the medication.
- In the event of subcutaneous/intramuscular delivery, less tissue irritation.
- The IV mode of administration can lead to rapid breakdown and tissue targeting
- Oral administration of Nano suspension results in a quick onset, a smaller fed/fasted ratio, and better bioavailability.
- By reducing the particle size, the uptake form absorption window may be expanded. It is suited for many methods of administration and can be included in tablets, pellets, hydrogel, and suppositories.
- A larger percentage of amorphous particles might affect the crystalline structure of the particles and increase solubility.
- Possibility of surface-modification for site-specific delivery of nanosuspension.
- It is possible to increase medication loading.
- Enduring chemical and physical stability (due to absence of Ostwald ripening).

DISADVANTAGES OF NANOCRYSTALS:[7,8]

- Compression, deposition, and physical stability can all be problematic.
- It requires careful handling and transportation because it is hefty.
- One cannot get a consistent and precise dosage.

PROPERTIES OF NANOCRYSTALS:[9]

- Increased Rate of Dissolution
- Enhanced saturation solubility
- Enhanced stability
- Enhanced permeability
- Increased adhesiveness

PREPARATION OF NANOCRYSTALS:

1. Bottom up technology

1.1 Anti-solvent precipitation

1.2 Supercritical fluids

1.3 Spray-drying

2. Top down Technology

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2.1.1. Bead milling

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1. BOTTOM UP TECHNOLOGY :

This technology's basic idea is based on precipitation by the drug is dissolved in a solvent, and the solvent is then added to a non-solvent, causing the precipitation of the small drug particle.

1.1 Anti-solvent precipitation[10]

In this method, the drug is dissolved in an organic solvent in which it is soluble, and the resulting solution is combined with an antisolvent that is miscible in order to precipitate the drug in the presence of a stabiliser. The drug's solubility in the water-solvent mixture is low, and it precipitates out. Additionally, high shear processing has been mixed with precipitation. Rapid precipitation in conjunction with high-pressure homogenization is used to achieve this. The healthcare company Baxter unveiled NANOEDGE, a patent with the number US 6,884,436. This method of technology uses high shear and/or thermal energy to precipitate friable materials for fragmentation. Rapid addition of the drug solution to the antisolvent results in the abrupt super saturation of the mixed solution and the formation of small crystalline or amorphous solids. To this a protective collide is added. An O/W two phase system is the result. The carotenoid that the colloid has stabilised localises in the oily phase. X-ray analyses after lyophilization reveal that 90% of the carotenoid is in an amorphous condition.

1.2 Supercritical fluids

Several processes, including the supercritical Antisolvent process, the rapid expansion of supercritical solution (RESS) process, and the precipitation with compressed antisolvent (PCA) process, are used to create nanoparticles. In the RESS approach, drug solution is expanded through a nozzle into supercritical fluid, precipitating the drug as small particles due to the supercritical fluid's loss of solvent power. Using this method, Young et al. produced cyclosporine nanoparticles with diameters ranging from 400 to 700 nm. The medication solution is atomized into the CO2 compressed chamber while using the PCA method. The solution becomes oversaturated when the solvent is removed, which leads to precipitation. In the

supercritical antisolvent procedure, the medication solution is introduced into the supercritical fluid, where it supersaturates and extracts the solvent. The main drawbacks of this procedure are that it uses dangerous solvents and a lot more stabilisers and surfactants than other approaches.

1.3 Spray-drying[11]

This technique is typically employed to dry liquids and suspensions. Solution droplets are sprayed in a conical or cylindrical cyclone from top to bottom and dried by hot air in the same direction to produce spherical particles. Spraying is done with an atomizer that quickly rotates and scatters the solution as a result of the centrifugal force. A peristaltic pump delivers the solution to the inner tube at a specific flow rate, and nitrogen or air at a constant pressure is sent to the outer tube. A nozzle provides spraying. Spraying reduces the size of the solution's droplets, which improves the surface area of the material that is drying and speeds up the drying process. It is possible to change the solution's concentration, viscosity, temperature, and spray rate, as well as its particle size, fluidity, and drying speed. This technique enhanced the bioavailability and dissolving rate of numerous medications, including hydrocortisone and COX-2 Inhibitor (BMS-347070).

2. Top down Technology

The "Top down Technologies" are the ways of disintegration and are favoured over the methods of precipitation.

2.1 Media milling

2.1.1. Bead milling:[12]

Liversidge et al. invented the technique first. In this process, high-shear media mills or pearl mills are used to create the nanosuspensions. A milling chamber, a milling shaft, and a recirculation chamber make up the media mill. Particle size reduction results from shear forces of impact caused by the movement of the milling medium, which can be formed of glass, zirconium oxide, or strongly cross-linked polystyrene resin. The milling media, also known as pearls, are rotated at a very high shear rate after being fed into the milling chamber along with the water, medication, and stabiliser. The milling procedure is carried out in a temperature-controlled environment. The impaction of the milling media with the drug produces high energy and shear pressures, which give the energy input to break the microparticulate drug into nano-sized particles. This results in the formation of nanosuspension or nanoparticles. Both micronized and non-micronized drug crystals can be successfully processed using the media milling technique. The milling beads are coated to lessen the number of contaminants brought on by erosion of the milling media. Two fundamental milling concepts exist. Either an agitator moves the milling medium, or the entire container is moved in a complicated motion that causes the milling media to move as a result. The amount of surfactant present, the drug's hardness, viscosity, temperature, energy input, and milling media size are only a few of the variables that affect the milling time. The milling period might run anything from 30 minutes to many days.

2.1.2. Dry co-grind

After dispersing in a liquid medium, poorly soluble medicines are dry ground with soluble polymers and copolymers to create stable nanoosuspensions. When pharmaceuticals like griseofulvin, glibenclamide, and nifedipine are ground with sodium dodecyl sulphate (SDS) and polyvinylpyrrolidone (PVP), colloidal particles are formed.

There have been many soluble polymers and co-polymers utilised, including PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and derivatives of cyclodextrin. Because of an improvement in surface polarity and a change from a crystalline to an amorphous drug, this approach was able to improve the physicochemical properties and solubility of pharmaceuticals that were poorly water soluble. Dry co grinding can be done quickly, affordably, and without the need of organic solvents.

2.2 High pressure homogenizations[13]

When producing nanocrystals using homogenization methods, there are three important technologies namely: Microfluidizer technology (Nanojet technology), Piston gap homogenization in aqueous media (Dissocubes® technology) and in water mixtures or in nonaqueous media (Nanopure® technology)

2.2.1. Homogenization in Aqueous media (Disso cubes)[13]

R.H. Muller created this technology in 1999, and DDS Gmbh obtained the initial patent before transferring it to Skype Pharmaceuticals.The APVMicron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany) and piston-gap homogenizers are two types of homogenizers. The drug and surfactant suspension is driven under pressure via a Nanosized aperture valve of a high pressure homogenizer in this procedure. This approach uses the cavitation concept for particle size reduction. The dispersion in a cylinder with a 3 cm diameter abruptly passes through a 25 m wide opening. The flow volume of liquid in a closed system per cross section is constant according to Bernoulli's law. At a diameter of 3 cm to 25 m, it causes a rise in dynamic pressure and a fall in static pressure below the boiling point of water.When the suspension exits the gap (a process known as cavitation) and normal air pressure is attained, gas bubbles that were formed when the water first started boiling at room temperature implode. The cavitation forces of the particles are strong enough to transform the drug's microparticles into nanoparticles. In this, the power density of the homogenizer, the quantity of homogenization cycles, temperature, and homogenization pressure are used to determine the final particle size of the drug nanocrystals.

2.2.2. Homogenization in Non Aqueous Media (Nanopure)[13]

This method uses water-free medium or water combinations to homogenise the suspension. Oils and oily fatty acids have a much higher boiling point than water and a much lower vapour pressure than water, making them ideal for the Dissocubes technology. Therefore, the static pressure decrease will not be adequate to start cavitation.

Patents describing the disintegration of polymeric material by high-pressure homogenization state that disintegration was facilitated by higher temperatures of roughly 80 °C, which cannot be used to thermo labile materials. The drug suspensions in non-aqueous media used in Nanopure technology were homogenised at zero degrees Celsius or even below, a process known as "deep-freeze" homogenization. The outcomes were equivalent to Dissocubes, so they can be utilised successfully.

2.2.3 Nanojet technology

The name of this technique is Nanojet or opposing stream technology.

This technique involves a chamber where a stream of suspension is separated into two or more sections called a microfluidizer. things collide when put under a lot of strain. Particle collision, shear forces, and cavitation forces are caused by this. Particle size reduction occurs as a result of the process' high shear force, which is caused by particle collision and high pressure. The M110L and M110S micro fluidizers are examples of equipment that apply this idea. Dearn used the micro fluidization technique to create atovaquone nanoosuspensions. The main drawback of this method is the high volume of passes through the micro fluidizer and the correspondingly higher percentage of microparticles found in the final product.

2.3 Emulsion solvent diffusion method

For pharmaceuticals that are soluble in either a volatile organic solvent or a partly water-miscible solvent, emulsions can be used as templates. These solvents can be utilised as the emulsion's dispersed phase. To create an emulsion, an organic solvent or combination of solvents containing the medication is distributed in an aqueous phase containing the appropriate surfactants while being stirred. High pressure homogenization was used to further homogenise the resulting emulsion. The emulsion was diluted with water and homogenised by a homogenizer after homogenization cycles in order to disperse the organic solvent and turn the droplets into solid particles. Since one particle develops in every emulsion droplet, it is possible to regulate the size of the Nanosuspension's particles by regulating the emulsion's size. When the surfactant composition is optimised, more organic phase is used, which ultimately results in more drug loading in the emulsion. Originally, organic solvents like methanol, ethanol, ethyl acetate, and chloroform were used. However, their application in standard manufacturing processes has been constrained due to environmental risks and worries about residual solvents endangering people. This technique was used to create nanosuspensions of ibuprofen, diclofenac, and acyclovir.

3. Combination technology

3.1 NANOEDGE® Technology[14]

Precipitation and homogenization have the same fundamental concepts as NANOEDGE. These methods work best when combined since it produces smaller particles with better stability faster. The NANOEDGE

technology can address the main issues with the precipitation method, such as crystal development and long-term stability. This method involves further homogenising the precipitated suspension to reduce particle size and prevent crystal formation. Solvents that are water-miscible, such as methanol, ethanol, and isopropanol, are used to precipitate in water. Although they can be tolerated to some amount in the formulation, it is preferable to totally eliminate those solvents. An evaporation stage to create a modified starting material devoid of solvent can be added for effective manufacture of nanosuspensions utilising the NANOEDGE technology, which is then followed by high-pressure homogenization.

3.2 SmartCrystal® Technology[14]

PharmaSol GmbH was the original developer of this technology, which Abbott eventually purchased. It is a collection of various combination processes from which different process iterations can be selected based on the physical properties of the medication (such as hardness). Spray-drying and HPH are combined in the technique H42. The preparation of the nanocrystals takes only a few homogenization cycles. Amphotericin B nanocrystals are produced by processes H69 (precipitation and HPH) and H96 (lyophilization and HPH) that have a size range of around 50 nm. Pre-milling and high pressure homogenization (HPH) were the two steps used by S. Kobierski et al. (2008) to generate nanocrystals. Hesperidin nanosuspensions for cosmetic use were created by a combination of ball milling and another technique.

4. Other methods

4.1. Solvent evaporation

This method involves creating polymer solutions in emulsions and volatile solvents. However, in recent years, dichloromethane and chloroform have been phased out in favour of ethyl acetate, which has a superior toxicological profile. On the evaporation of the solvent for the polymer, which is permitted to diffuse through the continuous phase of the emulsion, the emulsion is transformed into a suspension of nanoparticles. The manufacture of single emulsions, such as oil-in-water (o/w) or double-emulsions, such as (water-in-oil)-in-water, (w/o)/w, are the two basic ways for creating emulsions in conventional procedures. In order to evaporate the solvent using one of these techniques, high-speed homogenization or ultrasonication must first be performed. This solvent must then be continuously stirred magnetically at ambient temperature or under reduced pressure. The obtained solidified nanoparticles after ultracentrifugation were lyophilized after being cleaned with distilled water to get rid of any additions like surfactants. The polymer concentration, stabiliser concentration, and homogenizer speed all had an impact on particle size.

4.2. Sonocrystallization

Sonocrystallization is a revolutionary method for reducing particle size based on crystallisation utilising ultrasound.

Sonocrystallization uses ultrasonic energy with a 20–100 kHz frequency range to cause crystallisation. It increases the nucleation rate while also being a powerful tool for regulating the size distribution of the active pharmaceutical ingredient (API) and reducing its size. The majority of applications used ultrasound in the 20 kHz to 5 MHz range. It has also been investigated how to change the unfavourable properties of NSAIDs, namely their poor solubility and dissolution rate and subsequently their poor bioavailability.

4.3. Melt emulsification

The basic approach for creating solid lipid nanoparticles is melt emulsification. Ibuprofen nanosuspensions are initially made by Kipp and colleagues using the melt emulsification process. There are four steps to it. The stabilizer-containing aqueous solution is added before the drug. To create an emulsion, the solution is homogenised by a high-speed homogenizer after being heated to a temperature over the drug's melting point. Throughout the entire procedure, the temperature is kept above the drug's melting point. The emulsion is finally cooled to cause the precipitation of the particles. The concentration of the medication, the amount and kind of stabilisers employed, the cooling temperature, and the homogenization process are the key determinants of nanosuspension particle size.

4.4. Bottom-Up NanoCrySP Technology[15]

The National Institute of Pharmaceutical Education and Research (NIPER), G. Shete, Y. Pawar, et al., introduced a more modern technique to produce hesperetin nanocrystalline solid dispersion (NSD) utilising NanoCrySP technology: a brand-new bottom-up method for creating solid particles that uses spray drying

WO2013132457 A2 contains pharmaceutical nanocrystals that are spread throughout a matrix of small molecule excipients. Their research aimed to enhance the oral bioavailability and pharmacological activity of hesperetin nanocrystals produced by a brand-new bottom-up NanoCrySP Technology.

NSD was produced utilising spray drying with hesperetin and mannitol in a 1:1 ratio. The development of NSD is based on the classical nucleation theory, where mannitol served as a plasticizer, a crystallisation inducer, and a source of heterogeneous nucleation sites, all of which helped hesperetin crystallise. In the mannitol matrix, hesperetin was discovered to be present nanocrystals with an average crystallite size of 137 nm in NSD.

APPLICATIONS[16-19]

The NC method has a lot to offer in the area of pharmaceutical medication delivery in a number of different areas. As a result, examples of the already marketed NC products are given after a presentation of the broad adaptability of NCs to various administration routes and biological applications.

- The generation of hydrogen
- Removal of poisons and pollutants
- Diagnostic imaging • Biotags for identifying genes
- Drug production • Protein evaluation
- Flat-panel televisions
- Illumination
- Infrared and optical lasers
- Optoisolators
- Chips for magneto-optical memory
- Self-contained intelligent materials.
- Nanoscale fabric surface treatments or additives can assist materials resist wrinkling, staining, and bacterial development as well as offer lightweight ballistic energy deflection in personal body armour.
- Nanoscale materials are starting to make it possible to create washable, resilient "smart textiles" with flexible nanoscale sensors and electronics with the ability to monitor health, catch solar energy, and harvest energy through movement.
- Vehicles including automobiles, trucks, aircraft, boats, and spacecraft that are lighter might save a lot of fuel.

CONCLUSION

Nanotechnology has the potential to revolutionize our lives. This is because it presents almost unlimited potential to make remarkable changes in virtually all fields ranging from medicine, computer technology, construction, environmental remediation, food industry, to new energy sources. The advantages of nanocrystals in physical stability, high drug loading and relative ease of production bring attractive alternatives for delivery of poorly soluble drugs. Nanocrystal technology is evidently suitable for drugs with poor solubility. Drug nanocrystals can be applied to all poorly soluble drugs to overcome their solubility and bioavailability problems. The decrease in particle size to nanometre range contributes to the increased particle surface, curvature, saturation solubility, dissolution velocity and further acceptable bioavailability. Various applied and combination technologies are developed for the production of drug nanocrystals.

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