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Nanocrystals in Drug Delivery: An Innovative Approach

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ABSTRACT

Nanocrystallization is an innovative method for recovering poorly soluble drugs, adding the benefits of a carrier-free delivery system. This review provides a comprehensive analysis of nanocrystals with a focus on their clinical implementation. In addition, the overview focuses on clinically approved nanocrystals and their development. This review mentions the importance of nanocrystal drugs. Nanocrystals are aggregates of hundreds to tens of thousands of atoms that combine to form crystalline material called "clusters." They are used as a physical approach to alter and enhance the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used *in vivo* to protect drug moieties in the systemic circulation. Nanocrystal manufacturing methods are new technologies such as bottom-down, top-down, bottom-up, and spray drying. These approaches pave the way for the development of nanoscale objects that can perform multiple technical tasks. Nanocrystal formulations include several improvements in oral bioavailability, improved dose proportionality, reduced food impact, suitability for administration by all routes, and the possibility of sterile filtration by reducing the particle size range. There are important advantages. The choice depends on the site and the delivery of the drug to the site of action at a controlled and sustained rate. Here we review the formulation of nanocrystals, characterization, the impact of those properties, and various aspects of their pharmaceutical use in drug molecules and therapeutic gene delivery.

INTRODUCTION

Drug nanocrystals are pure solid drug particles with an average diameter of less than 1000 nm. The term drug nanocrystals refer to the crystalline state of individual particles, but can also be partially or completely amorphous, depending on the manufacturing process [1]. Nanocrystal formulations designed for oral administration have many advantages, including:

• Increased absorption rate,

• Improved oral bioavailability,

• Fast effect,

• Improved dose proportionality,

• Reduced dose required,

• Applicability to all routes of administration in any dosage form.

Unlike micronized drugs, nanocrystals can be delivered in multiple ways. Oral administration is possible in the form of tablets, capsules, sachets, or powders. If possible in the form of tablets. Due to the very small particle size, nanosuspension can also be given intravenously, which can reach 100 % bioavailability.

• Reduced fasting/eating variability,

• Rapid, easy, and cost-effective formulation development

• Possibility of high drug load (3040 %),

• Improved reliability. Nanocrystal technology results in an increase in dissolution rate as a function of increased surface area. This is achieved by reducing the particle size of the drug to the nanoscale while preserving the crystalline form of the drug [2].

• Improved stability. These are stable systems because stabilizers are used to prevent the reaggregation of the active ingredient during manufacturing. Suspensions of drug nanocrystals in liquids can be stabilized by the addition of detergents or polymers.

• Applicability to all poorly soluble drugs as all of these drugs can be broken down directly into nanometer-sized particles.

Special properties of nanosized drugs

Drug nanoparticles are the pharmaceutical principle of all poorly soluble drugs, which is the reason why the rate of dissolution is the rate-determining step of absorption and therefore the oral bioavailability is too low. According to Noyes Whitney's formula, increasing the surface area increases the rate of dissolution. What was often overlooked in the past is only the saturation solubility and kinetic solubility of nanoscale compounds are increased compared to micron particles. The basis for this is the Kelvin equation, which describes the vapor pressure as a function of the curvature of the droplets in the gas phase. Compared to micrometer crystals, nanocrystals are supersaturated solutions. This situation is metastable. That is, as a function of time, crystallization begins, large crystals settle, and the system returns to a thermodynamically stable state of saturation solubility of micrometer crystals. However, in general, the duration of this supersaturation is sufficient for oral absorption. Amorphous materials generally have higher saturation solubility than crystalline materials. e.g. The solubility of amorphous itraconazole is 60 times that of the crystalline state. Therefore, to achieve the highest supersaturation, the ideal drug nanoparticles should be amorphous, not crystalline (drug nanoparticles). A prerequisite for applying this approach is the ability to remain amorphous [2, 3]. However, it has been shown that it is possible to store amorphous or solid solutions for the shelf life of the drug (e.g. Pfizer's SDD technology).

NANOCRYSTAL PREPARATION METHODS

Today, several manufacturing methods have evolved and the implemented manufacturing methods of nanocrystal formulations can be classified into "bottom-up", "top-down", "top-down and bottom-up" and "spray drying". can. Bottom-up technology starts with the molecule. Active ingredient.

The substance is dissolved by adding an organic solvent and then the solvent is removed by precipitation. "Top-down" technology applies a dispersion process using different types of grinding and homogenization techniques. "Top-down" technology is more popular than "bottom-up" technology. It is called "nano-ization". In other words, it is the process of breaking down large crystal particles into smaller pieces. Both methods are used together in "top-down and bottom-up" technology. Spray drying is also a method of producing drug

nanocrystals, which is faster and more convenient than other methods [3, 4, 5].

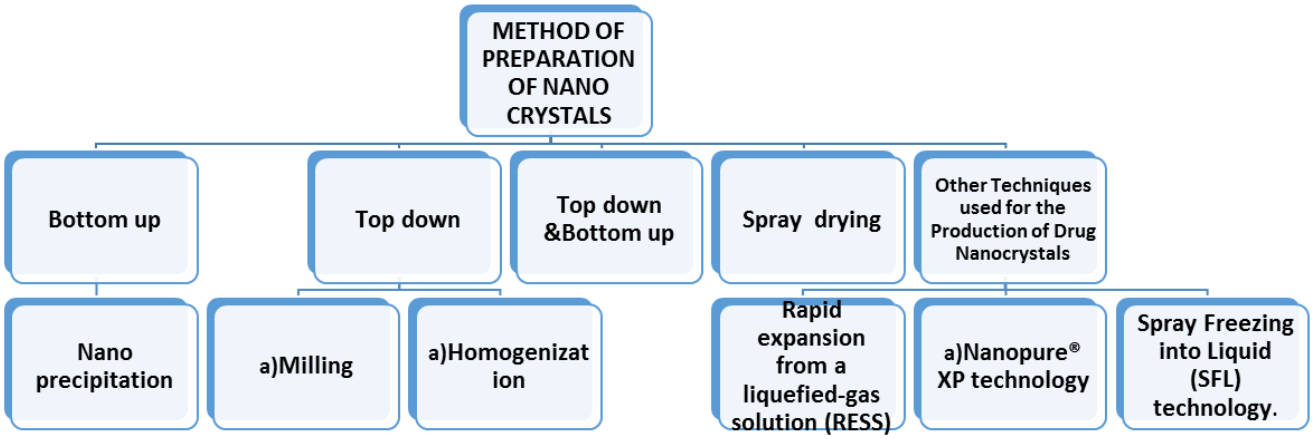

Figure No. 1:

1) **Bottom-up**

a) Nano precipitation

2) **Top-down**

a) Milling

b) Homogenization

3) **Top-down and Bottom-up**

4) **Spray drying**

5) **Other Techniques used for the Production of Drug Nanocrystals**

a) Rapid expansion from a liquefied-gas solution (RESS)

b) Nanopure® XP technology

c) Spray Freezing into Liquid (SFL) technology.

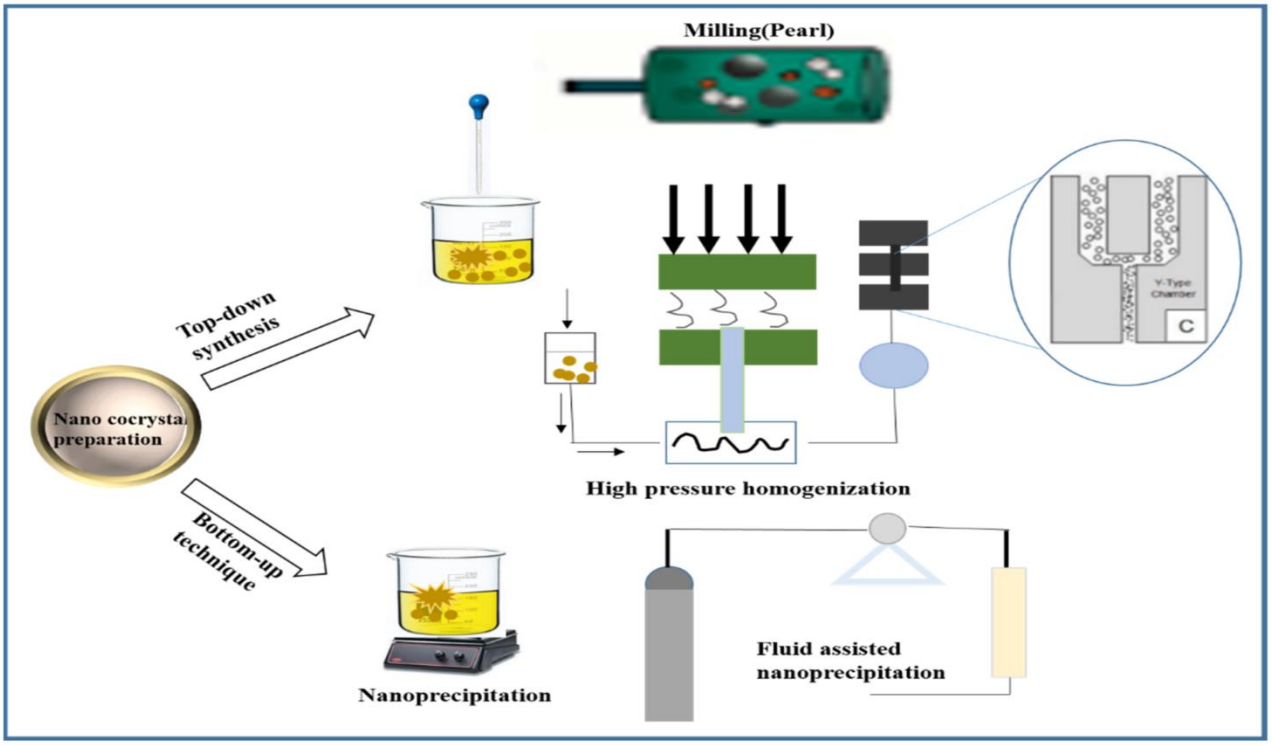

Figure No. 2:

Bottom-up technology

The principle of this method is based on the dissolution of the active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated. The basic advantage of the precipitation technique is that it is simple and has a low cost. Also, scale-up is simple in this method. It should be kept in mind that several parameters; such as stirring rate, temperature, solvent/ nonsolvent rate, drug concentration, viscosity, type of solvent, and stabilizer should be controlled to obtain homogenous nanocrystals by this technique [6]**.**

Nano-Precipitation process

Dissolving the drug in a solvent and then adding it to a non-solvent will precipitate finely dispersed drug nanocrystals. It should be noted that if these nanocrystals are not allowed to grow in the micron range, then these nanocrystals must be stabilized. In addition, the drug must be soluble in at least one solvent. This creates problems with newly developed drugs that are insoluble in both aqueous and organic media. For some of these reasons, this technology has not yet been applied to the product. The solution of surfactant and carotenoid indigestible oil is mixed with the appropriate solvent at a particular temperature. To obtain the solution a

protective colloid is added. This leads to an O/W two-phase system. The carotenoid stabilized by the colloid localizes in the oily phase. After Lyophilization X-ray analysis shows that approximately 90 % of the carotenoid is in an amorphous state [7].

Top-down technology

“Top-down” technology applies to disperse methods by using different types of milling and homogenization techniques. "Top-down" technology is more popular than "bottom-up" technology. It is known as "nano-ization". In other words, it is the process of breaking down large crystal particles into smaller pieces. Both methods are used together in "top-down and bottom-up" technology. Top-down techniques can be applied either by homogenization or grinding.

Milling Machine Process

Classic Nanocrystal® technology uses ball mills or bead mills to reduce particle size. Ball mills have been known for producing the finest suspensions since the first half of the 20th century. Grinding media, dispersion media (usually water), stabilizers, and drugs are charged into the grinding chamber. The impact shear force generated by the movement of the grinding medium leads to a reduction in particle size. In contrast to high-pressure homozygation, this is a low-energy grinding technique. Smaller or larger crushed beads are used as the crushing medium. The beads or spheres are made of ceramic (cerium-yttria-stabilized zirconia), stainless steel, glass, or beads coated with highly crosslinked polystyrene resin. Erosion of crushed material during the grinding process is a common problem with this technique. Grinding beads are coated to reduce the contamination caused by the erosion of the grinding medium. Another problem is that the product sticks to the inside of the mill. There are two basic grinding principles. The grist is agitated by the agitator, or the entire container is agitated with complex movements, resulting in the grist moving. Assuming that 76 % of the volume of the crushing chamber is filled with gravel, it is difficult to produce large batches when moving new vessels, so a large number of stirrer mills are used. Grind for large batches. Grinding time depends on many factors such as detergent content, drug hardness, viscosity, temperature, energy input, grinding medium size, and much more. Grinding time is about 30 minutes to hours or days. This new technology is a significant particle size reduction demonstrated by the four FDA-approved drugs described below in this text [8].

Homogenization methods

(IDDP ™ Technology) The Microfluidizer is a jet stream homogenizer in which two liquid streams collide head-on at high speeds (up to 1000 m/s) under pressures up to 4000 bar. Turbulence, high shear, and particle collisions reduce particles in the nanometer range. The high pressure applied and the high flow rate of lipids can also cause further cavitation, which contributes to size reduction. Stabilization with phospholipids or other surfactants and stabilizers is required to prevent particle size. In many cases, sufficient particle size reduction requires 50-100 time-consuming passes.

Underwater piston gap homozygation (Dissocubes®)

Drug nanocrystals can also be prepared by a high-pressure homogenizer using a piston gap homogenizer. Dissocubes® technology and Nanopure® technology are distinguished by the homozygation temperature and dispersion medium. The dispersion medium of the suspension was water. The piston of the large-diameter cylinder produces a pressure of up to 2000 bar. The suspension is pressed through a very narrow annular gap. The gap width is typically in the range of 315 microns at a pressure of 1500-150 bar [9, 10].

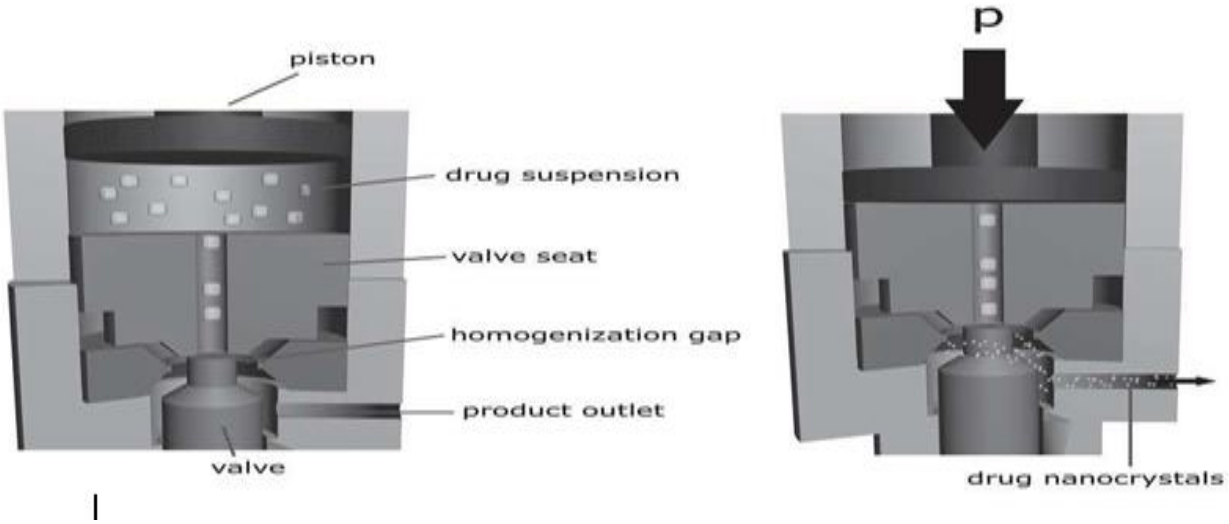

Figure No. 3: Basic principle of high-pressure homogenization using a piston gap Homogenizer

Top-down and bottom-up technology

Both methods are used together in "top-down and bottom-up" technology. NanoEdge® is a product obtained by such a combination technology. Nanoedge technology explained how to prescribe poorly water-soluble drugs. It is a useful technology for active ingredients with a high melting point and a high octanol-water partition coefficient. It is based on direct homozygation, microprecipitation, and lipid emulsions. In microprecipitation, the drug is first dissolved in a water-miscible solvent to form a solution. The solution is then mixed with a second solvent to form a presuspension and the presuspension is energized to form particles with an average effective particle size of 400 nm to 2 μm.

Spray drying

One of the methods for producing nanocrystals is spray drying. This method is commonly used to dry solutions and suspensions. In a conical or cylindrical cyclone, droplets of solution are sprayed from top to bottom and dried in the same direction by hot air to form spherical particles. Spraying is done using a nebulizer that spins quickly due to the centrifugal effect and sprays the solution. The solution is pumped to the inner tube at a specific flow rate using a peristaltic pump, and nitrogen or constant pressure air is fed to the outer tube. The spray is done through the nozzle. When sprayed, the droplets of the solution become very small. Therefore, the surface area of the desiccant increases, resulting in rapid drying. You can adjust the concentration, viscosity, temperature, and spray rate of the solution to optimize particle size, fluidity, and drying rate. The dissolution rate and bioavailability of several drugs, including hydrocortisone, a COX2 inhibitor (BMS347070), were improved using this method.

Other technologies [10, 11]

Rapid expansion from liquefied gas solution (RESS)

This method can be applied to substances that are soluble in supercritical fluids. In this process, the solute is first dissolved in a supercritical fluid and then passed through the nozzle at supersonic speeds. When the solution in the nozzle is decompressed, it expands rapidly.

Nanopure® XP technology

This is a registered product name of Pharma Sol GmbH / Berlin. Equally effective particle size reduction can also be achieved with non-aqueous or water-reduced media. Preparation of

nanocrystals in a non-homogenized medium is a very effective way to obtain a direct formulation. Nanocrystals of the active ingredient dispersed in liquid polyethylene glycol (PEG) or various oils can be filled directly into HPMC capsules or gelatin as an active ingredient suspension. Cavitation is the main force in reducing particle size. This technology was developed against this theory. Particle size reduction can also be achieved with non-aqueous media. It is necessary to form tablets, pellets, and capsules. The advantage of this process is that there is no need to remove the distributed medium. Evaporation occurs faster and under milder conditions (when using water and miscible liquids). This is useful for temperature-sensitive drugs. For IV Injection, isotonic nanosuspension is obtained by homozygation in a water-glycerol mixture. The reduction in water causes a reduction in the energy required for the various steps performed, such as fluidized bed drying, spray drying, or stratification of suspensions on sugar globules. Pharmasol's intellectual property includes water mixtures and anhydrous dispersion media (PEG, oil, etc.). NANOPURE® XP technology has the main features of scaling and the ability to produce on a large scale using mild and normal conditions. Pharmasol uses a pretreatment step followed by homozygation with NANOPURE® XP technology. This produces particles below the size range of 100 nm. The final nanosuspension looks translucent because the particle size is about 50 nm, which is smaller than the wavelength of visible light.

Spray freezing in liquid (SFL)

The University of Texas (Austin) was the first university to develop and patent the SFL method in 2003. This technology was first commercialized by the Dow Chemical Company (Midland, Michigan). As used herein, spraying of an aqueous, organic, aqueous organic co-solvent solution, aqueous organic emulsion, or suspension containing a drug is of a compressed gas (e.g. CO 2, propane, ethane, or helium) or a cryogenic gas. It happens directly to either. Liquid (e.g. argon, nitrogen, or hydrofluoroether).

Nanocrystal characterization

Particle Size Analysis

The size and size distribution of dry morphological crystals is redispersed in water containing 0.1 % polyvinyl alcohol (PVA and 403) and then dynamically light scattered by a particle size analyzer Nanotrac 150 (Japan) equipped with a wet sampling system. Determined by and the diameter was calculated from the reported average particle size distribution [12].

Determining drug content

The drug content of the lyophilized sample was checked using a UV and spectrophotometer to confirm the purity of the prepared sample. To quantify the drug content in the product, the aqueous dispersion of the product (25 mg/10 ml distilled water) was passed through a 0.8 µm filter. A filtrate containing fine particles smaller than 0.8 µm was dissolved in a 4% sodium lauryl sulfate solution, and the drug concentration was measured by spectrophotometry at a wavelength of 291 nm. The amount of drug infiltration relative to the total amount of drug in the dispersion was calculated and expressed as nanocrystal yield [13].

Scanning electron microscopy

The surface morphology of the commercial drug powder and the freeze-dried formulation samples was examined by SEM. Before examinations, the samples were mounted on top of double-sided sticky carbon tape on metal discs and coated with 80 nm Gold/palladium in Blazers 120B sputtering device.

Powder Xray diffraction (PXRD)

The XRD patterns were recorded on an X-ray diffractometer (PW 1729, Philips, Netherlands). Samples were irradiated with monochromatized Cu-Ka radiation (1.542A˚) and analyzed from 50 to 500 2θ. The voltage and current used were 30 kV and 30 mA, respectively. The XRD procedure to estimate the degree of crystallinity was based upon the measurement of the total scattering and the scattering from the crystalline region of formulations and pure drugs.

Differential scanning calorimeter

DSC, equipped with a liquid nitrogen cooling system was used to measure the thermal behavior of the commercial griseofulvin powder and the freeze-dried samples. For DSC analysis, 2 and 5 mg samples were placed in aluminum pans and tested at a scan rate of 100 ° C / min at 25-300 ° C.

Solubility

Saturation solubility measurements were examined by UV absorbance measurements at 291 nm using a UV spectrophotometer. Excess amounts of griseofulvin powder and the formulation were added to 150 ml of 4% SLS solution and the mixture was stirred in a

mechanical shaker at a temperature of 37 ± 0.05 for 24 hours.

° C, with GLF1086 shaker. Careful visual inspection was performed to confirm that the excess sample was present in the solid-state and reached saturation. The mixture was filtered using a 0.2 µm filter, the filtrate was diluted appropriately and the solubility of griseofulvin from each formulation was measured.

Dissolution test

Dissolution tests of griseofulvin and the pharmaceutical product on the market were performed by filling with Reinhard gelatin capsules (Zydus Cadila, Goa, India). The prepared sample and drug powder were packed in capsules (125 mg), subjected to a dissolution test using 900 ml of 4 % SLS solution as the dissolution medium, and preheated to maintain 37 ± 0.5 ° C. The basket was rotated at a speed of 75 rpm. Samples of at least 10 ml were taken at specific time intervals, filtered through a 0.2, and measured for concentration with UV and spectrophotometers [14].

Stability study

All formulations are tested for stability according to ICH guidelines and the formulations are divided into two parts, 30 ° C ± 2 ° C and 65% ± 5% relative humidity and 40 ° C ± 2 ° C and 70% ±. It was stored in. Store at 5% relative humidity. Drug release and drug content were estimated after a fixed time interval.

Application of nanocrystals to pharmaceuticals in drug development [15, 16].

1. Parent management

2. By oral administration

3. Administration of ophthalmic drugs

4. Delivery of the drug via the lungs

5. Targeted drug delivery

6. Skin administration of the drug

Parenteral administration

Drug nanocrystals in the form of nanosuspensions can be administered via a variety of parenteral routes of administration ranging from intra-articular to intra-articular. Intravenous injection from the abdominal cavity. Nanosuspension has been shown to enhance the effectiveness of parenteral drugs. Clofazimine nanosuspension, a less water-soluble anti-leprosy drug, is more stable and effective than liposomal clofazimine.

By oral administration

Nano sizing the drug dramatically improves oral absorption and subsequent bioavailability. Aqueous nanosuspension can be used directly in a liquid dosage form such as tablets and hard gelatin capsules with pellets.

Pulmonary drug delivery

Aqueous nanocrystals can be nebulized using mechanical and ultrasonic nebulizers for lung delivery. The dispersion can be of high concentration due to the presence of many small particles instead of a few microparticles; all aerosols` droplets are contained drug nanocrystals. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as nanosuspension is formulated for the treatment of lungs infections by using nebulization.

Target drug delivery

Nanocrystals can be used for target delivery. Targeting of *Cryptosporidium parvum*, the causative organism of cryptosporidium disease, was achieved using a surface-modified mucosal adherent nanosuspension of buplavauon. Similarly, diseases such as pulmonary aspergillosis can be easily addressed by using appropriate drug candidates such as amphotericin B in the form of lung nanosuspensions instead of stealth liposomes.

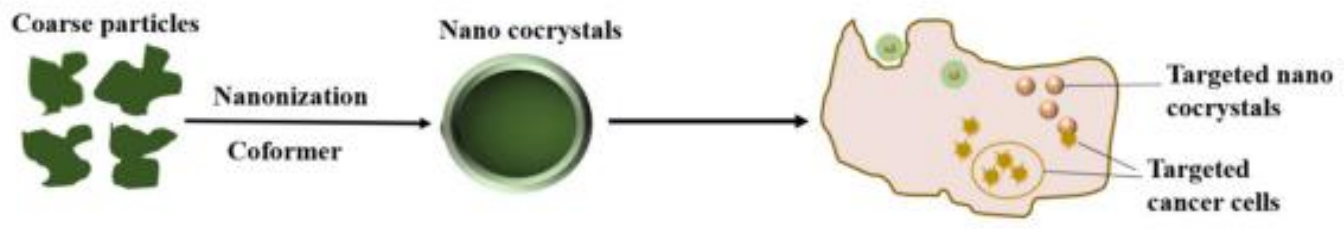

Figure No. 4:

Skin drug delivery

Skin nanosuspensions are of particular interest if the conventional formulation approach fails and the use of active ingredient nanocrystals leads to an increase in the concentration gradient between the formulation and the skin. Increased saturation solubility results in supersaturated formulations, thereby enhancing drug absorption through the skin. This effect can be further enhanced by using a positively charged polymer as a stabilizer for drug nanocrystals. Opposite charges lead to increased affinity of drug nanocrystals for negatively charged Stratum Conium.

CONCLUSION

Poor solubility is rapidly becoming a major hurdle for pharmaceutical scientists working on the oral delivery of drug compounds, leading to the use of new pharmaceutical technologies. The use of drug nanocrystals is a universal pharmaceutical approach to enhance the therapeutic performance of these drugs by any route of administration. Almost all drugs can be reduced in size to the nanometer range. Many insoluble drug candidates are prescribed as drugs in clinical trials. A significant advantage is that the drug nanocrystals can be applied to a variety of doses stretch. This means not only oral but also parenteral, especially intravenous administration, other administrations such as skin administration to create a supersaturated system with high thermodynamic activity. Ophthalmic delivery to create a system with extended retention time, nasal delivery to attach nanocrystals to the nasal mucosa, vaginal delivery to create a system that spreads evenly over the therapeutic area, and their inclusion criteria Aerosol-containing drug nanocrystals for pulmonary delivery based on. Drug nanocrystal technology is a successful new technology.

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