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NANOCRYSTAL AS DRUG DELIVERY SYSTEM

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ABSTRACT
A nanocrystal is a crystalline particle with at least one dimension measuring less than 1000 nanometres (nm), where 1 nm is defined as 1 thousand-millionth of a meter (10^{-9} m). Nanocrystals have a wide variety of proven and potential applications. Nanocrystals are pure drug crystals with sizes in the nanometer range stabilized or surrounded by a thin coating of surfactant. Nanotechnology has extensive application as nanomedicine in the medical field. Some nanoparticles have possible applications in novel diagnostic instruments, imagery and methodologies, targeted medicinal products, pharmaceutical products, biomedical implants, and tissue engineering. Application of nanotechnology leads to increase in bioavailability andbioactivity of phytomedicine by reducing the size of the particles, surface modification, attaching or entrapping the phytomedicine with different polymers of micro or nano materials. Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for the targeted delivery and controlled release of therapeutic agents. The modern form of a drug delivery system should minimize side-effects and reduce both dosage and dosage frequency.

KEYWORDS: Nanocrystals, Bioavailability, Nanotechnology, Side-effects.

1. INTRODUCTION

The basic elements of nanotechnology are nanoparticles. Nanoparticles are made of metal, metal oxides, organic materials, and carbon and range in size from 1 to 100 nm.[1] Surface can be irregular with surface variations or a uniform. Among nanoparticles some are crystalline or amorphous with single or multi-crystal solids either agglomerated or loose.[2] Nanoparticles differfrom various dimensions, to shapes and sizes apart from their material.[3] Pure solid drug particleswith a mean diameter of less than 1000 nm are known as drug nanocrystals. Since drug nanocrystals are encapsulating-carrier-free nanoparticles, they have the benefit of 100% drug loading. The medication and one or more stabilizers are disseminated in aqueous or non-aqueous fluids in the formulation of nanocrystals. One or more of the widely accepted safe excipients (Surfactants, buffers, salts, or sugars) could be stabilizers. Solid or sterile injectable dose forms could be created by further processing the liquid dispersion nanocrystals. It has been determined that products containing nanocrystals have therapeutic uses in the areas of targeted drug delivery, ophthalmic, cutaneous, parenteral, and oral administration. Unlike medications that are micronized, nanocrystals can be delivered through a number of paths. It is feasible to administer medication orally as tablets, capsules, sachets, or powder; the form of a tablet. Because of their extremely small particle size, nano suspensions can also be given intravenously, achieving 100% bioavailability in this manner. Drug nanocrystals are pure solid drug particles with a mean diameterbelow 1000 nm. The term drug nanocrystal implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. There are many advantages of nanocrystal formulations designed for oral administration and they are as follows.

- Increased rate of absorption.
- Increased oral bioavailability.
- Rapid effect.
- Improved dose proportionality.
- Reduction in required dose.
- Applicability to all routes of administration in any dosage form.

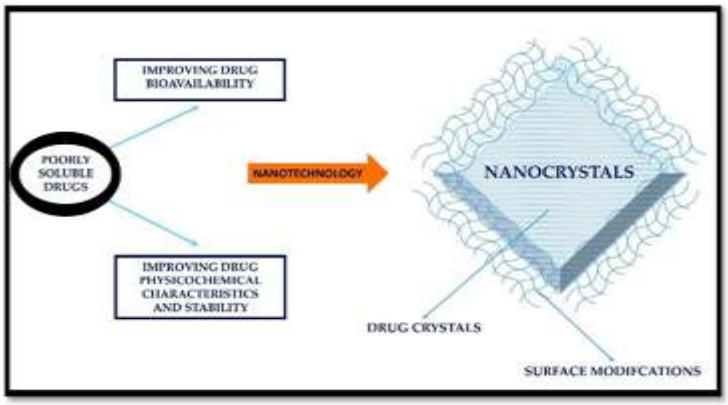

Figure 1: (Role of nanotechnology in bioavailability).

Contrary to micronized drugs, nanocrystals can be administered via several routes. Oral administration is possible in the form of tablets, capsules, sachets or powder; preferably in the form of a tablet. Nano suspensions can also be administered via the intravenous route due to very small particle size, and in this way, bioavailability can reach 100%.

- Reduction in fed/fasted variability,
- Rapid, simple and cheap formulation development
- Possibility of high amounts (30-40 %) of drug loading,
- Increased reliability.

Nanocrystal technology leads to an increase in dissolution rate depending on the increase insurface area obtained by reduction of the particle size of the active drug substance down to the Nano size range preserving the crystal morphology of the drug.

- Improved stability. They are stable systems because of the use of a stabilizer that preventsre-aggregation of active drug substances during preparation. Suspension of drug nanocrystals in liquid can be stabilized by adding surface active substances or polymers.
- Applicability to all poorly soluble drugs because all these drugs could be directlydisintegrated into nanometer-sized particles.

2. Preparation of nanocrystals

The therapeutic result of nanocrystal medication products is influenced by properties including crystallinity, size, shape, surface charge, and the kind of stabilizers or polymer coatings utilized during formulation. Additional physicochemical characteristics are presently being studied to seeif they have an impact on preclinical performance tests, or in vivo and in vitro tests. Add surface texture and hardness as well. Medication nanocrystals were nearly entirely composed of medication, with very little stabilizing agent present. Stabilizers were anchored to the surface of the drug nanocrystals through ionic or steric stabilization. In order to prepare drug nanocrystals, it is crucial to choose the right medications and stabilizers. Typically, medications that are lipophilic or weakly soluble in water are chosen and stabilized. The most common components of stabilizersare: (1) polymers, like sodium dodecyl sulfate (SDS), polyvinyl pyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC); (2) ionic surfactants; and (3) non-ionic surfactants, like tweens and poloxamers (polyoxyethylene–polyoxypropylene copolymers). Different interaction forces work between stabilizers and drug nanocrystals. For example, ionic surfactants use electrostatic repulsion to stabilize drug nanocrystals, whereas polymers and non-ionic surfactants use steric repulsion to coat drug nanocrystals.[4] There are three primary ways to synthesize medicinal nanocrystals: top-down size techniques include combination, bottom-up (nucleation and growth), and reduction of big drug particles.

3. Various methods of nanocrystal preparation

There are various methods developed to prepare drug nanocrystals. The milling processes includedisintegration and homogenization by the use of mechanical forces to disintegrate active pharmaceutical ingredients into nanosized particles. Using this method, there are a number of commercial products available in the market and has been approved by regulatory bodies. However, these types of methods utilize high energy, or pressure to produce nanoscale size. In addition, mechanical attrition leads to some associated drawbacks such as high energy use, time- consuming and no control on particle size, and electrostatic effects. In the crystallization method of preparation, there is minimum mechanical energy used to prepare the nanocrystals. The crystallization method involves the following steps: (1) dissolution; (2) nucleation; (3) growth of the crystals; and (4) filtration followed by drying. Furthermore, various crystallization techniques such as supercritical fluid, high gravity, cryogenic techniques, ultrasonication, and microemulsion methods were used to produce the nanocrystals. The preparation techniques used to create nanocrystal formulations nowadays can be categorized as "bottom up," "top-down," "top down and bottom up," and "spray drying." "Bottom Up" technology starts with the molecule, dissolves the active ingredient in the medicine by adding an organic solvent, and removes the solvent by precipitation. "Top down" technology uses various homogenization and milling processes to apply dispersing strategies. The term "nanosizing" refers to the

fact that "top down" technology is more common than "bottom up" technology. Stated differently, it is a process that reduces huge crystalline particles to smaller ones. In "top down and bottom up" technology, the two approaches are combined. Another quicker and more useful technique for creating medication nanocrystals is spray drying.

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.

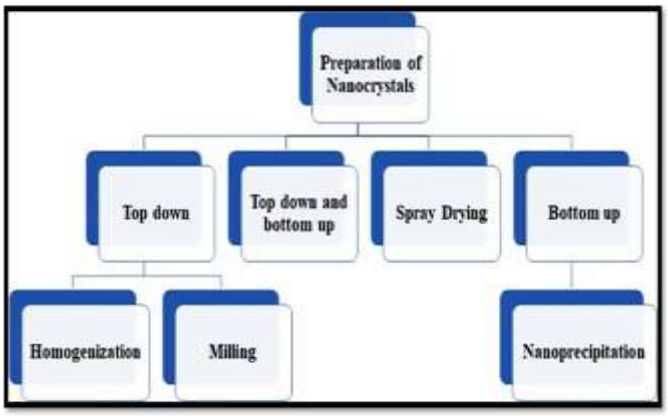

Figure 2: (Preparation of nanocrystal).

(a) Bottom-up technology

This method's basic idea is to dissolve the active ingredient in an organic solvent, then mix it with a non-solvent that is miscible with the organic solvent. The nanocrystals then precipitate in the presence of stabilizers. The precipitation technique's primary benefits are its affordability and ease of use. This method's scaling up is also straightforward. It should be noted that in order to achieve uniform nano crystals using this process, a number of parameters need to be regulated, including temperature, stirring rate, solvent/nonsolvent rate, drug concentration, viscosity, type of solvent, and stabilizer.

(b) Top down technology

"Top-down" technology applies dispersing methods by using different types of milling and Homogenization techniques. "Top-down" technology is more popular than "Bottom up" technology; it is known as "nanosizing". In other words, it is a process which breaks down large crystalline particles into small pieces. In "top Down and bottom up" technology, both methods are utilized together. Top- down technology can be applied by either homogenization or milling. Top-down approach refers to the particle size reduction of coarse drugs down to nanoscale drug crystals by milling or high-pressure homogenization (HPH) methods. In milling method, four forces, such as shearing, attrition, impact, or pressure, are involved to pulverize the coarse drugs, and wet ball milling (bead or pearl milling) is the most frequently used method in the pharmaceutical industry. This method will generally yield well- defined drug nanocrystals with a narrow size distribution after enough time of milling. Besides milling, the HPH technique is using jet-stream homogenization of drugs, dispersion medium, surfactants, and/or stabilizers under high pressure through a very thin gap (typically about 25 µm) at an extremely high velocity. The particle size reduction of drug nanocrystals, caused by cavitation forces, shear forces and collision during multiple homogenization cycles, is dependent on many factors such as the types of homogenizers, pressures, and cycles. In HPH method, the size distribution of drug nanocrystals is strongly dependent on the brittleness, hardness, and defect density of the initial drug crystals.

Besides milling and HPH methods, laser fragmentation was also used to prepare drug Nanocrystals by focusing a femtosecond or nanosecond laser radiation on a magnetically stirred drug suspension in water or aqueous solution of a stabilizing agent. For example, PTX43 and megestrol acetate (MA) have been fragmented into nanocrystals by using this method. For the synthesis of MA nanocrystals, the femtosecond laser fragmentation was performed with vertical configuration, and the nanosecond laser fragmentation was performed with horizontal configuration. Compare with untreated water-exposed, ~30% and ~60% of the MA mass was <1 µm after the femtosecond and nanosecond laser treatments, respectively. The scanning electron microscope (SEM) observation is in agreement with size distribution analysis by dynamic light scattering (DLS) in. Besides the high energy input and high risk of contamination, both of above top-down methods cannot produce small size drug nanocrystals (< 100 nm). Therefore, other methods are actively developed to address these issues.

(c) Top Down and Bottom up technology

In "top down and bottom up" technology, both Methods

are used together. Nano-Edge® is a product Obtained by such a combination technology. Nano- edge Technology described the formulation method for poorly Water-soluble drugs. It is a useful technology for active Ingredients that have high melting points and high Noctanol-water partition coefficients. It is based on direct Homogenization, micro precipitation, and lipid emulsions. In micro precipitation, the drug first is dissolved in a Water- miscible solvent to form a solution. Then, the Solution is mixed with a second solvent to form a pre- Suspension and energy is added to the pre suspension to Form particles having an average effective particle size of 400 nm to 2 µ.

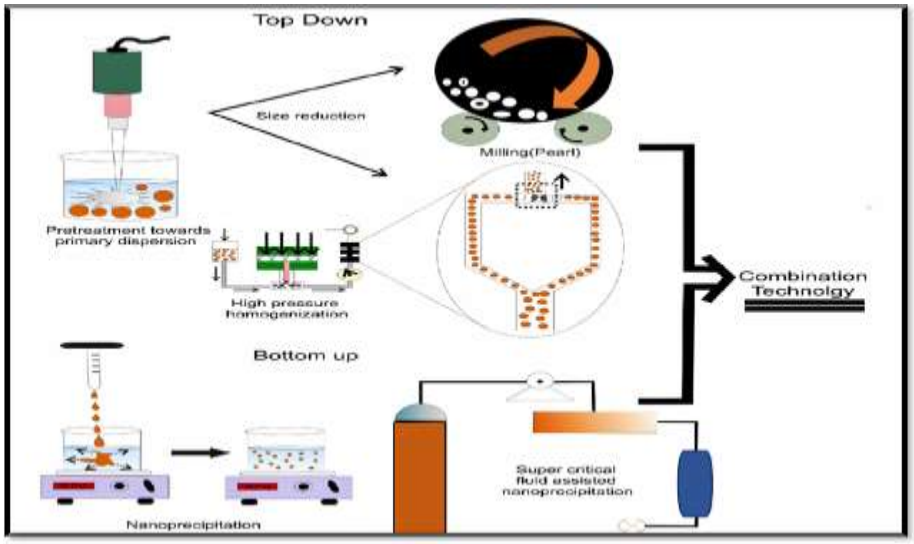

Figure 3: (Process of nanoprecipitation / Preparation of nanocrystals).

(d) Spray drying

Spray drying is one way that nanocrystals are prepared. Typically, this technique is employed to dry solutions and suspensions. Solution droplets are sprayed from top to bottom in a conical or cylindrical cyclone, dried in the same direction by hot air, and spherical particles are produced. Anatomizer that spins quickly is used to spray; the solution is scattered because of the centrifugal force. Using a peristaltic pump, the solution is delivered to the inner tube at a specific flow rate, while nitrogen or air is delivered to the outer tube at a steady pressure. A nozzle is used to deliver spraying. Spraying reduces the size of solution droplets, increasing the drying matter's surface area and accelerating drying.

(e) Combination method

Top-down and bottom-up approaches were combined to produce medicine nanocrystals with a tiny(< 100 nm) and narrow size distribution and get over the problems associated with lengthy production timeframes. Additionally, combination procedures have been developed that combine a high energy step (such as HPH) with a pre-treatment step. These days, top-down methods such as combination technology (media milling followed by HPH), NANOEDGE54 (micro- precipitation followed by HPH), and H 69 (micro-precipitation immediately followed by HPH, also known as "cavi-precipitation") are used first as a pre-treatment and then as a top-down method for further homogenization. Nanosuspensions containing nanocrystals are unstable in a liquid environment due to the Ostwald ripening and settling process; thus, procedures such as H 42 (spray-drying followed by HPH) and H 39 are used for additional solidification.

4. Characterization of nanocrystals

For the successful fabrication of a nanocrystal formulation, besides selection of the appropriate excipients, equally important is the characterization of the formulation to ensure that the necessary parameters responsible for the performance of nanocrystals are within the specified limits. The following sections discuss in detail the various characterization tests for the evaluation of nanocrystals.

(a) Solid state properties

The degree of crystallinity, polymorphic crystal shape, and solvate form—particularly hydrate form—of the solid state all affect perceived solubility and, in turn, the rate of dissolution. Determining these properties in nanocrystals is therefore essential. The most stable crystalline structure that is thermodynamically possible is preferred in order to minimize the risk of solid state changes during manufacturing, storage, and/or administration.

The resulting solid state form may differ depending on the conditions and methods used during the manufacture of nanocrystals. The environmental factors also influence the polymorphic form that is thermodynamically stable. For instance, in aqueous conditions, hydrate forms are often less soluble and more stable.

(b) Thermal analysis

One frequently used technique for examining the thermal behavior of drugs and drug nanocrystals is differential

scanning calorimetry (DSC). Following the creation of nanocrystals, DSC investigations are carried out to assess the drug's crystallinity and the interaction between the drug and excipients. This is particularly crucial for medications that are found in many polymorphic shapes. Furthermore, some top-down methods, such as high pressure homogenization, can produce particles with an amorphous proportion, which can improve solubility at saturation.[5] Heat is delivered to the sample and reference pan via the thermoelectric disk when the furnace is heated at a linear rate. However, there would be a difference in temperature between the sample and reference pans due to the sample's heat capacity (Cp) of the sample, there would be adiscrepancy in the temperature between the sampleand reference pans, which is measured by areathermocouples, and the consequent heat flow isdetermined by the thermal equivalent of Ohm's law: q= ΔT/R where q is "sample heat flow", T is "temperature difference between sample and reference", and R is "resistance of thermoelectric disk". In a power-compensated DSC, the sample and reference pans are placed in separate furnaces heated by separate heaters. The sample and reference pans are maintained at the same temperature, and the difference in thermal power required to maintain themat the same temperature is determined and plottedagainst temperature or time.[6,7]

(c) X-ray Diffraction (XRD)

When a medicine is converted to a nanocrystal formulation, X-ray diffraction investigations aretypically carried out to confirm the drug's crystallinity. An X-ray's interaction with a crystalline material results in a diffraction pattern. In a mixture of substances, each develops its pattern independently of the others, and every crystalline substance yields a distinct pattern that is alwaysthe same. A substance's distinct fingerprint is thus represented by its X-ray diffraction pattern. In order to examine how the drug's crystalline structure changed after it was transformed into nanocrystals, the authors used XRD. Furthermore, the spray-dried Nano suspension created by top-down technique (high speed milling) powder XRD examination revealed a little shift in the major peaks in comparison to the pure drug. In addition, the powder XRD study of spray dried Nano suspension prepared by top-down process (high speed milling) showed negligible shift in the main peaks as compared to pure drug. The characteristic peaks for milled and unfilled drug were observed at the same 2θ values. A slight decrease in intensity of peaks was observed with spray dried Nano suspension operated at higher milling speed.[8]

(d) FT-IR Studies

FT-IR investigations are used to assess the chemical characteristics of the medicine and its interaction with excipients. Landing and associates Curcumin nanocrystals were developed and assessed by al. for pulmonary administration. The generated dry powder inhalation (wet millingfollowed by spray drying) and the pure drug were subjected to FTIR experiments to assess any changes in the medication's chemical characteristics.[9]

(e) Raman spectroscopy

Raman spectroscopy is a spectroscopic technique based on inelastic scattering of monochromaticlight, originating from a laser source. Inelastic scattering means that the frequency of photons in monochromatic light amends following interaction with a sample. Photons of the laser light are absorbedby the sample and then reemitted. Frequency of the reemitted photons is shifted up or down compared to that from the original monochromatic frequency.

The size of nanocrystals in this process was influencedby factors such as the freezing rate. Hence, to determine during what stage of the process the solutescrystallized and how the freezing rate impacted the particle size, the crystallization process was monitoredby Raman Spectroscopy.[10] Liquid atomization-based techniques, like spray drying or electro spraying, are markedly susceptible togenerating a final product in the amorphous form(partially or fully). However, full crystallinity can be obtained after production by annealing. The high shearstresses associated withwet media milling and high-pressure homogenization may also result in polymorphic changes.[11] Nanocrystals were produced by wet ball milling, with poloxamer188 used as a stabilizer. Therewere no significant differences between the particle size of thetwo polymorphs when the same milling protocol was used, but differences in the stability with respect to theparticle size were seen during the 90 days of stability testing. The milling did not alter the polymorphic formof the drug. The crystallite size of the milled polymorphs was calculated based on XRPD peak width broadening. It was observed that for polymorph1, the crystallite size was around 90 nm while for polymorph 2 it was around 65 nm.[12]

(f) Particle Size and Size distribution

Size and size distribution are important characterizations of the Nano suspensions because they direct the other properties, such as physical stability, saturation solubility and dissolution velocity, and evenclinical efficacy. The smaller the particle size, the higher the surface energy of the particles, which promotes aggregation. The most frequently used techniques for particle size measurements ofnanosized systems are dynamic light scattering techniques, static light scatteringtechniques and microscopy. The polydispersity index (PI) value ranges from 0(monodisperse particles) to 0.500 (broad distribution), and is a crucial index that governs the physical stability. For a long-term stability the PIshould be as low as possible. Techniques for the detection of larger particles are optical microscopy and low angle static light scattering (laser light diffraction), especially for the Nano suspensions that are meant for parenteral and pulmonary delivery. The Laser diffractometric (LD) yields a volume distribution and possesses a measuring range of

approximately 0.05–80 µm up to a maximum of 2000µm, depending on the type of equipment employed. Typical characterization parameters of LD are diameters 50%, 90%, 99%, represented by D50, D90, and D99, respectively (i.e., the D50 implies that 50% of the volume of the particles is below the given size). The disadvantages of laser diffraction techniques rosewith the need of analyzing nanoparticles with a technique being originally intended for the measurement of largerparticles in the micron range. Since laser diffraction is a simple and rapid method itwas aimed to extend the measuring range (e.g., from 400 nm to 2000 m) to a broader range, being able to analyze even very small particles (e.g., from 20 nm to 2000 m) py, and scanning tunneling microscopy.[13]

(g) Particle Shape and Morphology

Ideally, a transmission electron microscope (TEM) or a scanning electron microscope (SEM) can be used to determine the shape or morphology of the nanocrystals. A appropriate concentration of a wet sample is required for the TEM analysis. To monitor changes in the shape and size of the particles before and after the water removal process, a SEM examination is essential when the formed Nano suspensions are to be dried into a powder (e.g., by spray drying or lyophilization).[14] A type of scanning probe microscope called atomic force microscopy (AFM) uses a probe to assess local characteristics including height, friction, and magnetism.[15] Surface plasmon resonance (SPR) analysis has been employed in interaction studies between solid drug surfaces and aqueous stabilizer solutions. Five structurally different PPO/PEO block co-polymers were used as stabilizers for indomethacinnanocrystals, and affinities between the stabilizers andsolid drug surfaces were determined by SPR and contact angle measurements.[16] Particle shape is of prime importance when thenanocrystals are to be formulated as dry powder inhalers (DPIs) for direct lung delivery of the drugs. Particle interactions are linked to the van der Waalsforces, which are the particle surface morphology, size, shape, properties. Particle shape that possess low contactarea and van der Waals force have a lower tendency toaggregate and hence can be readily dispersed in the air. Elongated particles are not ideal for aerosolization owing to their large attractive forces.[17]

(h) Particle surface charge

The surface charge of the particles is one of the factorsinfluencing the physical stability of Nano suspensions. The higher the particles are equally charged, greater is the electrostatic repulsion between the particles and greater is the physical stability. The particle surface charge is ideally quantified in terms of the "zeta potential", which is measured via the electrophoretic mobility of the particles in an electric field. The particle charge can be measured in surface charge perunit, determined by colloid titration.[18,19] In an electrolyte containing media, ions from the dispersion medium adsorb onto the particle surface. For this model description a negative Nernst potential is assumed. In general, the first absorbed monolayer ofions comprises of negatively charged, fixed and dehydrated ions, termed as the Helmholtz layer. The measurement itself is a particle electrophoresis, the particle velocity is determined via the Doppler shift of the laser light scattered by the moving particles. The field strength applied is generally 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz–Smoluchowski equation. At standard measuring conditions (room temperature of 25 ◦C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (µm/cm per V/cm) by a factorof 12.8, yielding the ZP in mV.[20,21]

(i) Dissolution of nano crystal

Apparent Solubility and Supersaturated State Thermodynamic solubility implies the solubility of themost stable crystalline form of the drug in a givenmedium at a specified pressure and temperature. Solubility can temporarily be higher than thethermodynamic solubility. This may be observed withamorphous forms, metastable polymorphic forms, ornanosized drug particles. This enhanced solubility hasbeen designated with diverse terms, such as kinetic orapparent solubility.[22] The thermodynamic solubility of the bulk drug inaqueous 0.5% and 1% sodium dodecyl sulfate solutionwas 6.02 and 23.54 µg/mL, respectively, while the corresponding values for drug nanocrystals were 67.51 and 107 µg/mL, respectively.[23] The intrinsic dissolution rates were profoundly influenced by the particle size and the stabilizer. Withthe smallest nanocrystals (580 nm), the intrinsic dissolution rate with poloxamer F68 as a stabilizer was0.50 µg/min/mm^2, while that for poloxamer F127 was0.31 µg/min/mm^2. The dissolution rate of bulkindomethacinwas also determined and found to be considerably lower at 0.05 µg/min/mm^2. Surface concentrations have also been measured with UV- imaging. Indomethacin, the model drug used was found to interact with both the type of filter tested as well as thecentrifuge tube material. Undissolved drug particles inthe sample can be recognized employing multiplewavelengths for the analysis.[24] The parachute effect of the polymer can be due to a combination of mechanisms. First, the polymers can themselves increase the thermodynamic solubility of the drug (also termed as the co-solvency effect), whichlowers supersaturation and consequently the thermodynamic driving force for crystallization (this also leads to an additional spring effect with the polymer). Through drug-polymer interaction in solution via electrostatic bonds, van der Waals' forcesor hydrogen bonding, even the addition of small amounts of polymers such as PVP and HPMC tosolution can significantly increase the aqueous solubility.[25]

(j) Permeation study

Nanocrystal based drug delivery could be very effective for improving dermal bioavailability of drugs with poor solubility. Indeed, in addition to increased saturation

solubility and dissolution rate, nanocrystal also exhibits the property of increased adhesiveness tothe skin thus facilitating the dermal delivery. The twomechanisms by which drug is delivered to the skin; first one is simple increase of concentration gradient between formulation and skin and the second mechanism involves hair follicles. Nanocrystals with an appropriate size (approximately 700 nm) can deposit into these shunts, which act as a depot from which the drug can diffuse into the surrounding cells for extended release.[26,27] The nanocrystal based drug delivery to the eye can be exploited for improving retention and penetration of drug in to the eye. The possible mechanism for this is not only to increase solubility in lachrymal fluid but also to produce adhesive properties. Nanocrystals maybe used not only to increase solubility in lachrymal fluids of poorly soluble drugs, but also to produce adhesive properties (determined by the nature of the surfactant in the formulation) that can be exploited forimproving the retention and penetration ofdrugs into the eye. Non-ionic surfactants are preferred over ionicbecause they are generally lessirritating. The permeation studies are usually done by using the Franzdiffusion cell apparatus.[28]

Pharmaceutical applications of nanocrystals in drug delivery[29,30]

1. Parental administration.
2. Per oral administration.
3. Ophthalmic drug delivery.
4. Pulmonary drug delivery.
5. Target drug delivery.
6. Dermal drug delivery.

1. **Parenteral administration:** Drug nanocrystals in the form of nanosuspensions can be administered via Different parenteral administration route ranging from intra articular via. Intraperitoneal to intravenous injection. Nanosuspension has been found to increase the efficacy of Parenteral administered drugs. Clofazimine nanosuspension, poorly water soluble anti leprosy drug, reveals an improvement in stability and efficacy over the liposomal Clofazimine.

2. **Per oral administration:** Nanosizing of drug leads to dramatic increase in their oral absorption and subsequent bioavailability. Aqueous nanosuspension can be used directly in liquid dosage form such as tablets and hard gelatin capsule with pellets.

3. **Pulmonary drug delivery:** Aqueous nanocrystals can be nebulizer using mechanical and ultrasonic nebulizers for lung delivery. The dispersion can be high concentration due to the presence of many small particles instead of a few micro particles; all aerosols droplets are contain drug nanocrystals. Budesonide, poorly water soluble corticosteroid, has been successfully prepared as nanosuspension is formulated by treatment of lungs infections byusing nebulisation.

4. **Target drug delivery:** Nanocrystals can be used for target delivery. Targeting of cryptosporidium partum, the organism responsible for cryptosporidiosis was achieved by using surface modification mucoadhesive nanosuspension of bupravauone. Similarly, condition such as pulmonary aspergillosis can easily targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspension instead of using stealth liposome.

5. **Dermal drug delivery:** Dermal nanosuspension are mainly of interest if conventional formulation approaches fail the use of drug nanocrystals leads to an increased concentration gradient between the formulation and the skin. The increased saturation solubility leads to supersaturated formulations, enhancing the drug absorption through the skin. This effect can further be enhanced by the use of positively charged polymers as stabilizers for the drug nanocrystals. The opposite charge leads to an increased affinity of the drug nanocrystals to the negatively charged stratum cornium.

Properties of nanocrystals

The main reasons for the increased dissolution velocity and thus increased bioavailability are

Increase of dissolution velocity by surface area enlargement

The size reduction leads to an increased surface area and thus according to the Noyes-Whitney equation (Noyes and Whitney 1897) to an increased dissolution velocity. Therefore micronization is a suitable way to successfully enhance the bioavailability of drugs where the dissolution velocity is the rate limiting step. By moving from micronization further down to nanonization, the particle surface is further increased and thus the dissolution velocity increases too. In most cases, a low dissolution velocity is correlated with low saturation solubility.

Increase in saturation solubility

The general textbook statement is that the saturation solubility cs is a constant depending on thecompound, the dissolution medium and the temperature. This is valid for powders of daily life with a size in the micrometer range or above. However, below a critical size of 1–2 μm, the saturation solubility is also a function of the particle size.

It increases with decreasing particle size below 1000 nm. Therefore, drug nanocrystals possessincreased saturation solubility. This has two advantages

1. According to Noyes and Whitney (1897), the dissolution velocity is further enhanced becausedc/dt is proportional to the concentration gradient (cs-cx)/h (cs- saturation solubility, cx - bulk concentration, h - diffusional distance).

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

Advantages of nanocrystal formulations

- Increased rate of absorption,
- Increased oral bioavailability,
- Rapid effect,
- Improved dose proportionality,
- Reduction in required dose,

- Applicability to all routes of administration in any dosage form. Contrary to micronized drugs, nanocrystals can be administered via several routes. Oral administration is possible in the form of tablets, capsules, sachets or powder; preferably in the form of a tablet. Nanosuspensions can also be administered via the intravenous route due to very small particle size, and in this way, bioavailability can reach 100 %.
- Reduction in fed/fasted variability,
- Rapid, simple and cheap formulation development.
- Possibility of high amounts (30-40 %) of drug loading,

- Increased reliability. Usually side effects are proportional to drug concentration, so decreasing the concentration of active drug substances leads to an increased reliability for patients.[32]

- Sustained crystal structure. Nanocrystal technology leads to an increase in dissolution rate depending on the increase in surface area obtained by reduction of the particle size of the active drug substance down to the nano size range preserving the crystal morphology of the drug.[33]

- Improved stability. They are stable systems because of the use of a stabilizer that prevents reaggregation of active drug substances during preparation.[34] Suspension of drug nanocrystals in liquid can be stabilized by adding surface active substances or polymers.

- Applicability to all poorly soluble drugs because all these drugs could be directly disintegrated into nanometer-sized particles.

Disadvantages of nanocrystals

Toxicity: The use of nanoparticles in medicine is still a relatively new field, and there is limited knowledge on their long-term toxicity. Studies have shown that some nanoparticles can accumulate in the body and cause damage to organs and tissues.[35]

Cost: The development and production of nanoparticles can be expensive, which could limit their availability and affordability.

Regulatory challenges: The use of nanomedicine in humans is subject to strict regulatory approval, which can slow down the development and implementation of new therapies.[36]

Ethical concerns: There are also ethical concerns surrounding the use of nanomedicine, particularly in areas such as genetic engineering and enhancement.[37]

Limited knowledge: There is still a lot to learn about the interactions between nanoparticles and the human body. More research is needed to fully understand the potential benefits and risks of nanomedicine.[38]

Table 1: (Advantages and disadvantages of nanocrystals).

Technology	Advantages	Disadvantages
Precipitation	1) Finely dispersed drug Good control of desired size	1) Need to be stabilized 2) Organic solvent residue 3) Not universally applicable, only drugs with certain properties are possible (eg- soluble in at least one solvent)
Milling	1) Low energy technique 2) Proven by 4FDA approveddrug.	1) Residue from millingmedia2) Can be slow process(several days) 2) Needs to be stabilized 3) Larger batches difficult toproduce due to size of milling chamber
Homogenization	1) Universally applicable 2) No problem with largerbatches 3) Fast method 4) Water free productionpossible	1) High energy technique 2) Great experience needed

Table 2: (Various researches on drug formulation by nanocrystal).

Sr. No.	Title	Reference
1	Formulation & evaluation of imipenem loadedcalcium carbonate nanocrystal hydrogel.	VB, BS. Formulation & evaluation of imipenem loaded calcium carbonate nanocrystal hydrogel., 2023; (9): 1325-1335.
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18	Nasal delivery of nanosuspension – based mucoadhesive formulation with improved bioavailability of loratadine: preparation, characterization, and in vivo evaluations.	Areen alshweiat, Ferenctomosis, tamas Janky, Anita Kovacs, Robert Gaspar. Nasal delivery of nanosuspension – based mucoadhesive formulation with improved bioavailability of loratadine: preparation, characterization, and in vivo evaluations, 2020; 579.
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5. CONCLUSION

For formulation scientists working on the oral administration of therapeutic molecules, poor solubility is quickly rising to the top challenge, necessitating the use of innovative formulation technologies. Using medication nanocrystals is a common formulation strategy to boost the therapeutic effectiveness of these medications whether administered via any method. It is possible to shrink almost any medication down to the nanoscale. A large number of insoluble drug candidates are being developed as drugs in clinical studies. One of the most notable benefits is that the medication nanocrystal can be administered through a variety of methods. This refers to the use of oral, parenteral, particularly intravenous, and other forms of administration, such ascutaneous distribution, to produce a super-saturated system with a high degree of thermodynamic activity. Nasal administration to adhere nanocrystal to the cornea, and ocular administration to develop systems with extended retention time.

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