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Production, Characterization, Application and Current Development of Nanocrystals: an Overview

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ABSTRACT:
Drug nanocrystals are the latest, broadly introduced nanoparticulate carrier to the pharmaceutical market from the year 2000 onwards.Nanocrystals have the potential to address challenges in very different fields like production of computer chips, delivering drugs of low water solubility, cosmetic research and products, biotechnology, catalysis and textile.Nanocrystals (NCs) are the class of solid dosage forms which utilizes the concept of nanoscience together with crystal nature of drug to achieve advantages in terms of solubility, dissolution, and physicochemical properties. Comparing with other solid dosage forms, NC often comes with so many challenges in terms of physical stability as well as chemical stability during the manufacturing process and storage.Nanocrystals aid the clinical efficacy of drugs by various means such as enhancement of bioavailability, lowering of dose requirement, and facilitating sustained release of the drug. This effect is dependent on the various characteristics of nanocrystals (particle size, saturation solubility, dissolution velocity), which have an impact on the improved performance of the nanocrystals.In this review, we highlight the industrially relevant technologies, milling, high-pressure homogenization, characterization of nanocrystal, application in pharmaceutical industryand the special features of nanocrystals for the delivery of poorly soluble drugs are briefly reviewed.

KEYWORDS: Nanocrystals, Milling, Homogenization, Nanotechnology, Bottom up, Solubility.

I. INTRODUCTION:

"Today nanotechnology is encountered all around our daily lives. Whether it's in the production of computer chips (where the need for more integrated circuits per square millimeter is evident to produce chips with more computing power" [1]), "the growing field of biotechnology (where new tools to easily interact with proteins in ever smaller sizes are required" [2]), or simply cosmetic research and products (where the need for new tools to easily interact with proteins in ever smaller sizes is required [3]), or simply cosmetic research (where nanonized agents can provide a whole range of benefits [3]).

Because of the vast range of potential uses in cosmetics, computing, semiconductors, pharmaceuticals, and biomedicine, nanocrystal production has attracted a lot of attention. "Nanocrystals are used in a wide range of cosmetic goods, including moisturisers, deodorants, toothpaste, make-up, and sunscreen. Nanocrystal products have been found as next-generation cosmetic delivery agents capable of improving skin hydration and bioavailability" [4]. Medication nanocrystals have been one of the most widely debated drug delivery strategies in the last two decades. Drug nanocrystals, unlike other nanoparticulate systems, are mostly made up of pure API.

Nanonization (i.e., reducing the size of a substance to less than 1000 nanometers) is a major aspect in current medication delivery and clinical applications, both today and in the future. The formation of poorly water-soluble pharmacological moieties is currently the most difficult task facing formulation experts. The growth of high throughput screening methods has led to an increase in the number of newly discovered medications with low water solubility.

"According to reports in the literature, more than 40% of medicines entering the formulation development pipeline have low water solubility" [5]. Poor water solubility is linked to low bioavailability. If there is no way to increase medication solubility, the medicine will not be able

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to pass through the gastrointestinal tract and reach the site of action.

"Many ways have been investigated in the attempt to improve bioavailability. Most of these approaches, however, are limited to medications with a specific chemistry (i.e., solubility in specific organic solvents) or a specified molecular size/shape or conformation" [6].

Furthermore, the use of surfactants is a possible alternative, albeit surfactant toxicity may be an issue. Many poorly water-soluble medications in BCS Classes 2 and 4 have had their bioavailability issues solved by developing the drug into nanosized formulations. Nanoscaled drug particles stabilized by an appropriate stabilizer or surfactant, referred to as "Nanocrystals," are one type of nanosized formulation. Drug nanocrystals are crystals with dimensions in the nanometer range, often ranging from a few nanometers to 1000 nanometers."Nanosuspensions" are drug nanocrystals that have been dispersed in an aqueous media. The advantage of nanocrystals is that they are made entirely of medicine, unlike polymeric/lipidic nanoparticles, which have a carrier component. They are commonly made by precipitating the drug from its organic solvent and then adding an aqueous surfactant/stabilizer solution, or by exposing the drug's macrosized dispersion to intense particle size reduction procedures while still containing a surfactant/stabilizer.

NCs' nanometer size allows for significant improvements in solubility and dissolution, making it easier to improve the efficacy of poorly soluble medicines supplied via intravenous, oral, ophthalmic, pulmonary, and transdermal routes. Furthermore, the NCs beat conventional carrier-based nanomedicines such as liposomes, dendrimers, and micelles attributed to their promising stability, ease of scale-up, exceptionally high drug loading (theoretically 100 percent), and lower toxicity.

Special features of nanocrystals:

1. increased saturation velocity.
2. increased dissolution velocity.
3. increased adhesiveness to surfaces/cell membranes.

Nanocrystals are created from poorly soluble pharmaceuticals; medications that are water soluble cannot be manufactured into nanocrystals (at least not in aqueous dispersion medium). Poorly soluble medications can be formulated as nanocrystals to overcome biopharmaceutical delivery issues., e.g.

- Too low bioavailability after oral administration,
- Too low penetration into the skin (low dermal bioavailability),
- Too large injection volume for i.v. administration, and
- Undesired side effects after intravenous injection when using traditional formulations (e.g., solutions with solubilized drug).

II. METHOD OF PRODUCTION OF NANOCRYSTALS:

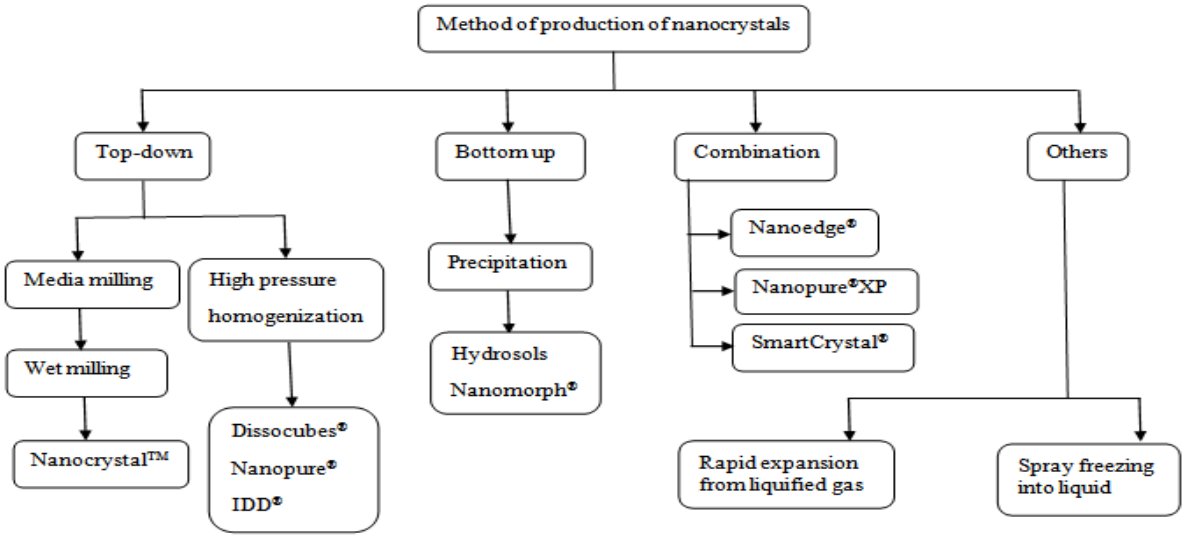

Fig 1: Diagrammatic representation of method of production of nanocrystals

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The most significant technique for producing nanocrystals is the top-down approach. Milling and high-pressure homogenization are the two most common top-down size reduction procedures. Wet milling has produced the greatest number of nanocrystal products.

Wet milling is used because dry milling is ineffective in obtaining nanometer-sized particles. Wet milling is a process that involves dispersing medication particles in a surfactant/stabilizer solution and then grinding the resulting macrosuspension.

For the homogenization method, there are three important technologies to produce nanocrystals which are Microfluidizer technology, Piston-gap homogenization in water and Piston-gap homogenization in water mixtures or in nonaqueous media.

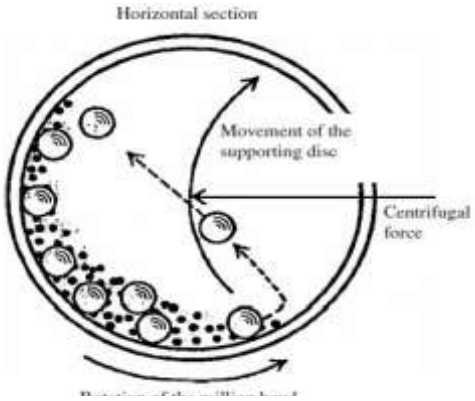
(2.1.1) Wet ball milling-

The most common process for producing medication nanocrystals in the pharmaceutical industry is wet ball milling (also known as pearl milling or bead milling). Because the milling method is quite straightforward, it may be carried out in almost any laboratory. Low energy ball milling (LE-WBM) with a jar filled with milling medium is the simplest technique to do WBM (often just very simple glass beads). This system is charged with a coarse drug material, preferably micronized, suspended in a dispersion medium with at least one stabilizing agent. By using an electric stirrer to move the beads, or by moving the whole jar, e.g., with a roller plate or a mixer, the milling beads can interact with the drug particles. Atthe beginning of the nineties, very similar set-ups were used in order to establish this technology for pharmaceutical purposes. The relatively low energy input leads to very long milling times of several days [7].

"The technique's principal drawbacks are contamination from metal milling balls or pearls, high energy input, lengthy operation time, and lower crystallinity" [8]. The usage of polymeric beads could help to reduce erosion and contamination.

"To make this method more appealing for industrial pharmaceutical applications, alternative milling procedures based on high energy processes had to be developed. The NanoCrystalTM process in its current form is based on such a high energy wet ball milling process (HE-WBM)" [9].

Fig 2. High energy ball milling procedure for nanocrystal synthesis.



(2.1.2) High pressure homogenization-

HPH can be regarded as the second mostimportanttechnique to produce drug nanocrystals. The broad acceptance of this approach is supported by many examples from the literature.

"The process of high-pressure homogenization is when two fluid streams of particle suspensions come into conflict in a chamber under high pressure, causing particle collision and subsequent particle rupture. Piston-gap homogenizers create nanosized solid particles by pressing a suspension of drug particles through a thin gap under high pressure with a piston" [10].

The particles are dispersed by strong shear forces and turbulent flow, and the particle outcome is determined by the power of homogenization, particle hardness, and number of piston-moving cycles. "High-pressure homogenization requires a high process temperature, high energy input, sophisticated equipment, and the potential for component deterioration and lower yields when compared to wet milling, which are the technique's key limitations" [11].

The particle size reduction itself is caused by cavitation forces, shear forces and collision. In general, several homogenization cycles are needed to reach the minimal particle size. The number of passes (i.e., homogenization cycles) depends on many factors.

Parameters that influence homogenization
1 Applied pressure
2 number of homogenization cycles
3 temperatures

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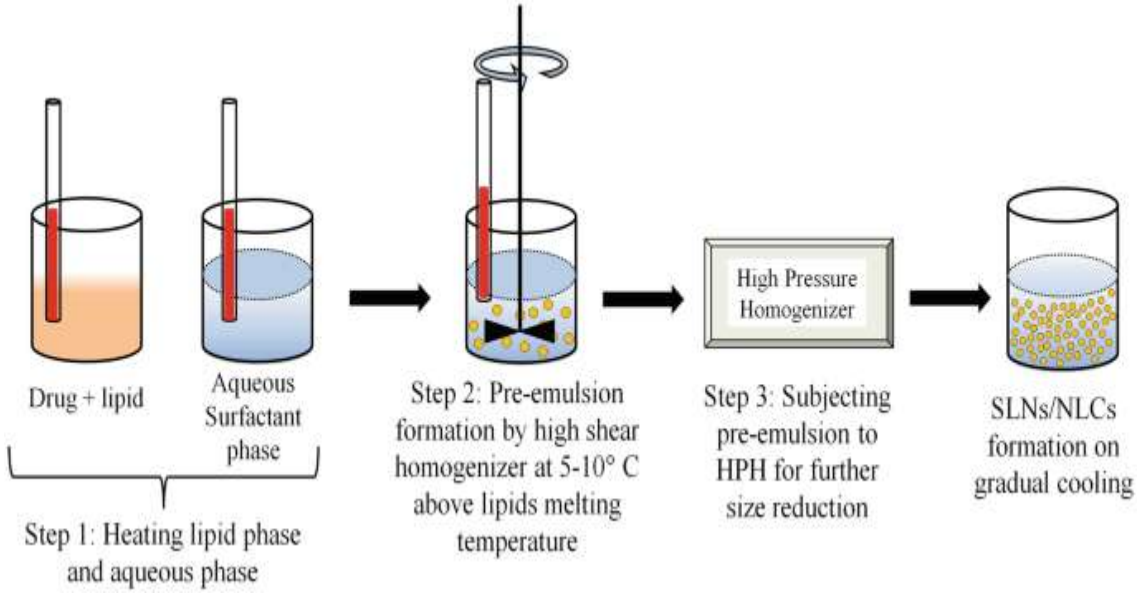
"HPH is a scalable process, which is applied not only in the pharmaceutical but also in the cosmetics and food industry" [12].

Fig 3. High pressure homogenization techniques for nanoparticles.



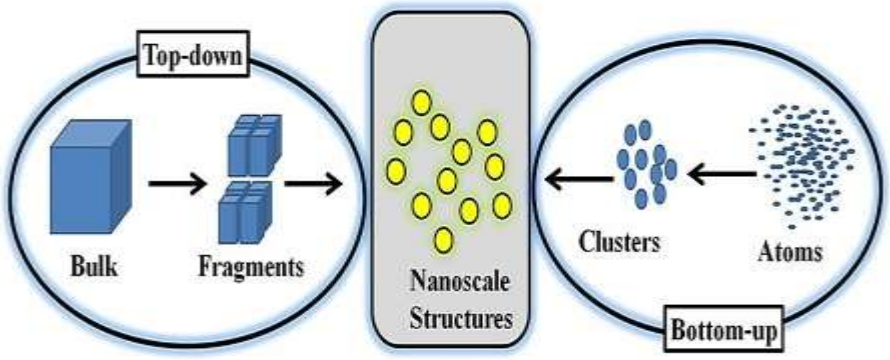
1.1 Bottom-up process-

Starting with a molecule in solution, bottom-up processes aggregate molecules into particles, which can be crystalline or amorphous. It's a typical precipitation event (in latin: via humida paratum, prepared in a wet process). The basic concept is that the medication is dissolved in a solvent, and then the solvent solution is introduced to a non-solvent, causing the drug to precipitate. Optimizing the particle structure (amorphous versus crystalline) and avoiding crystal development to the lm size range are critical in this technique.

"There are various other bottom-up technologies, e.g., the highgravity-controlled precipitation technology, sonocrystallization, confined impinging liquid jet precipitation and multi-inlet vortex mixing, for a detailed review it is referred to" [13].

Many precipitation operations depend on organic solvents, which must be eliminated in the majority of cases, raising expenses. Especially when substantial solvent volumes are needed, like when the medication has a low solubility in both water and organic solvents. As a result, top-down technologies are frequently used in the pharmaceutical industry for newly released products.

Fig 4. Nanocrystal synthesis by top-down and bottom-up process.



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1.2 Combination process-

Although the standard technologies WBM and HPH are now widely acknowledged and used, there are still some drawbacks that have been solved through continuous process development. Another drawback of traditional techniques is the relatively long processing times. This is in contrast to the 30–120 minutes required by WBM to make nanosuspensions. However, this is the shortest duration a medicine can be in contact with the grinding chamber. When a large-scale mill is operated in re-circulation mode, the suspension is exposed to high energy only when it passes through the milling chamber.As a result, depending on the ratio between total batch volume and milling chamber volume, overall production time is significantly longer. In the case of HPH, the condition is similar. High-pressure homogenizers on the market can process 1000 l of nanosuspension or more in 1 hour. If 20 homogenization cycles are necessary to obtain a specific particle size, the total process time for batches of 1000 l can easily exceed 20 hours unless more homogenizers are employed in series.

"Alternative processes have been developed to overcome the above-mentioned drawbacks. A pre-treatment step is usually followed by a high-energy process in combination technologies. Baxter developed the NANOEDGE™ technology. Crystals are precipitated in the first phase, and the resulting suspension is subsequently subjected to a high-energy process, such as high-pressure homogenization" [14].

Table 1. Methods of preparation of nanocrystal of particular drugs

Sr no	Drug	Method of preparation
1	Ketoprofen	Media milling
2	Naproxen	spray drying
3	Amioderon	supercritical fluid technology
4	Piroxicam	High pressure homogenization
5	Phenytoin	Rapid supercritical expansion
6	Ketoprofen	Milling
7	Itroconazole	Pearl milling
8	Curcumin	High pressure homogenization
9	Betulin	Antisolvent precipitation
10	Glibenclamide	Combination
11	Nebivolol	Acid base neutralization
12	Refampicin	Wet media milling
13	Aceclofenac	Precipitation unltrasonication
14	Nifedipine	High pressure homogenization
15	Amitriptyline	Spray freeze drying
16	Carvedilol	High pressure homogenization
17	Cyclosporine	High pressure homogenization
18	Glipizide	Media milling
19	Greseofulvin	Emulsion solvent diffusion
20	Indinavir	Supercritical antisolvent
21	Indomethacin	Wet ball milling
22	Lansprazole	Solvent evaporation
23	Lovastatin	Precipitation unltrasonication
24	Mebendazole	Wet bead milling
25	Nelfinavir	Combination method
26	Ritonavir	High pressure homogenization
27	Spironolactone	Wet milling
28	Ciprofloxacin	Spray drying
29	Mebendazole	Wet bead milling
30	Acetazolamide	Antisolvent precipitation

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A stable Nanosystem should posses

1. **Appropriate zeta potential-** The zeta potential requires a minimum absolute value of 30 mV. In combination with steric stabilization, an absolute of the zeta potential of approximately 20 mV is sufficient to stabilize fully a nanocrystals system. The suitable zeta potential acquired by using different stabilizers.
2. **The effect of stabilizers on nanocrystals-** Stabilizers usually produce ionic or steric stabilization by covering the surface of nanoparticles. Polymer steric stabilization is suitable for the stabilization of drugs during the preparation process compared to the conventional surfactants of small molecular weights.

Stabilizers affect the absorption process of nanocrystals or other drug delivery systems and may function through mechanisms such as:

a) increasing the saturation solubility and dissolution rate
b) enhancing mucoadhesion
c) opening tight junctions and enhancing permeability
d) inhibiting the P-gp efflux
e) enhancing cellular uptake.

3. **Crystalline state-**The difference in crystalline states may cause variations in bioavailability. The effect of polymorphs on the bioavailability of poorly soluble drugs has already been studied and several drugs, such as carbamazepine and phenylbutazone have exhibited differences in bioavailability between different crystalline states.

4. **Shape of crystal-** Differences in shapes may cause differences regarding the in vivo performance of nanocrystals, and the influence of different shapes on the absorption of nanocrystals have been studied.

III. 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

(3.1) Thermal Analysis-

One widely used techniques for examining the thermal characteristics of drugs and drug nanocrystals is differential scanning calorimetry (DSC). DSC tests are used to evaluate the drug's crystallinity and the interaction of excipients with drug following nanocrystal formation. This is especially true for medications that come in multiple polymorphic forms. Furthermore, some top-down processes, such as high-pressure homogenization, might result in particles with an amorphous component, increasing saturation solubility. “DSC is performed on a pure drug, a physical mixture of the drug and excipients (stabilizer), and the final formulation, which may be in dried form. DSC is divided into two categories based on its operation mechanism: heat flux DSC and power compensated DSC. In heat flux DSC, two pans are placed on a thermoelectric disk surrounded by a furnace containing sample and empty reference pan. The furnace is heated at a linear heating rate, and the heat is transferred to the sample and reference pan through the thermoelectric disk” [15-17].

Hot stage microscopy (also known as Thermal Microscopy or Thermomicroscopy) is a combination of microscopy with thermal analysis that allows for the study and physical characterization of materials as a function of temperature and time, among other thermal techniques. Hot stage microscopy is useful for identifying the crystalline and amorphous regions of nanocrystals as well as screening and characterization of polymorphs.

(3.2) Solid State Properties-

The visible solubility and thus the dissolution rate are influenced by solid-state features (polymorphic crystal form, solvate (particularly hydrate) form, degree of crystallinity). As a result, determining these properties in nanocrystals is critical. To avoid the dangers of solid-state changes during production, storage, and/or administration, the thermodynamically most stable crystalline form is preferred. It is better to manufacture nanocrystals in a metastable crystalline form or even prepare the amorphous analog of nanocrystals to increase solubility and bioavailability. However, this is not a universal practice.

X-ray powder diffraction (XRD), thermal analytical techniques (differential scanning calorimetry, thermogravimetry, etc.) and vibrational spectroscopy (infrared and Raman) are

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the most commonly used methods to determine and monitor the solid-state form of nanocrystals.

(3.3) X-ray Diffraction (XRD)-

X-ray diffraction studies are widely used to confirm drug crystallinity after it has been converted to a nanocrystal formulation. A diffraction pattern is formed when X-rays contact with a crystalline substance. Every crystalline substance creates a unique pattern; the same substance produces the same pattern every time; and in a mixture of substances, each ingredient makes its own pattern independently of the others. The X-ray diffraction pattern of a substance thus displays the substance's unique fingerprint.

(3.4) FT-IR Studies-

FT-IR studies are used to assess the chemical characteristics of drugs and their interactions with excipients. Curcumin nanocrystals for pulmonary administration were developed and tested by Liandong et al. "The change in chemical characteristics of the medicine was evaluated using FTIR measurements of the pure drug and the generated dry powder inhalation (wet-milling followed by spray-drying). Milling and spray drying did not modify the chemical composition of curcumin, according to the position of IR peaks in the formulation compared to the pure drug" [18].

(3.5) Raman Spectroscopy-

Raman spectroscopy is a spectroscopic technique that relies on the inelastic scattering of monochromatic light emitted by a laser source. The frequency of photons in monochromatic light changes due to inelastic scattering when they interact with a material. The sample absorbs photons from the laser light, which are then reemitted. The reemitted photons' frequency is shifted up or down in comparison to the monochromatic frequency. The "Raman Effect" is the name given to this phenomenon. This shift reveals information on low-frequency vibrational, rotational, and other transitions in molecules.

(3.6) Particle Size and Size Distribution-

The size and size distribution of nanosuspensions are significant characterizations because they influence other parameters like physical stability, saturation solubility and dissolution velocity, and even therapeutic efficacy. "The surface energy of the particles increases as their size decreases, promoting aggregation. Dynamic light scattering techniques, static light scattering techniques, and microscopy are the most often used techniques for particle size measurements of nanosized systems. Dynamic light scattering, also known as photon correlation spectroscopy (PCS), is commonly used to determine the mean particle size of nanosuspensions" [19].

It offers the advantages of providing accurate results as well as quick and simple measurement. This approach, however, cannot be used to evaluate particles larger than 6 mm. Aside from the mean particle diameter, PCS can also produce the "polydispersity index," which is the width of the particle size distribution (PI). The physical stability is governed by the PI value, which varies from 0 (monodisperse particles) to 0.500 (wide distribution). The PI should be as low as possible for long-term stability.

(3.7) Particle Surface Charge-

One of the factors that contributed the physical stability of nanosuspensions is the surface charge of the particles. The greater the electrostatic repulsion between the particles and the greater the physical stability, the higher the particles are evenly charged. The "zeta potential," which is assessed by the electrophoretic mobility of particles in an electric field, is an ideal way to quantify particle surface charge. Colloid titration can be used to calculate the particle charge in surface charge per unit.

"The dissociation of surface functional groups, referred to as the Nernst potential, inherently gives particles a surface charge. Because the degree of dissociation of the functional groups is affected by the pH of the solution, zeta potential is a pH-dependent property. The storage stability of submicron colloidal dispersion can be predicted using zeta potential measurements" [20,21].

(3.8) Permeation Study-

Drug delivery using nanocrystals could be particularly effective in enhancing topical bioavailability of medicines with low solubility. Indeed, in addition to improved saturation solubility and dissolving rate, nanocrystal also has a higher adhesiveness to the skin, making dermal distribution easier. The first mechanism includes a simple rise in the concentration gradient between the formulation and the skin, while the second method involves hair follicles. Nanocrystals of a suitable size (about 700 nm) can be deposited into these shunts, which operate as a depot from which the drug can diffuse into the surrounding cells for prolonged release.When a poorly soluble medication is designed for topical drug delivery,

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aspects such as drug crystal particle size, carrier surface qualities, and drug-stabilizer interaction must be considered.

The use of nanocrystal-based drug delivery to the eye can be used to improve drug retention and penetration. "Nanocrystals can be used to increase the solubility of poorly soluble medications in lachrymal fluids, as well as to provide sticky characteristics (defined by the nature of the surfactant in the formulation) that can be used to improve drug retention and penetration into the eye. Nonionic surfactants are preferable to ionic surfactants because they are less irritating" [22].

(3.9) Dissolution study-

The most stable crystalline form of the medication in each medium at a given temperature and pressure is indicated by the thermodynamic supersaturated state and apparent solubility. Different terms for this increased solubility include apparent and kinetic solubility. Dissolution of nanocrystalline material results in the production of a supersaturated solution because apparent solubility of nanosized particles is higher than thermodynamic solubility of material. The "spring effect" is the name for this occurrence. "Ige and his colleagues investigated the saturation solubility of fenofibrate nanocrystals with a size reduction from 80 to 460 nanometers.The thermodynamic solubility of the bulk drug in 0.5% and 1% sodium dodecyl sulfate solution was found to be 6.02 and 23.54 μg/mL, respectively while the drug nanocrystals showed the solubility of 67.51 and 107 μg/mL, respectively" [23].

IV. APPLICATION AND ROUTES IN DRUG DELIVERY BY NANOCRYSTALS [23]-

(4.1) Oral Drug Delivery-

In comparison to other administration methods, the oral route is the most preferred and safest. It improves bio adhesion in the intestinal wall, resulting in increased oral bioavailability of poorly soluble medicines. Calculating pharmacokinetic parameters including maximum plasma concentration (Cmax), time to reach maximum concentration in plasma (Tmax), and area under the blood concentration-time curve can help assess bioavailability (AUC).

"Danazol nanocrystals, for example, were synthesized from micron-sized particles and exhibited a 16-fold increase in bioavailability over the pure medication. Nanocrystals improve uniform distribution in the GIT and minimize local extended concentrations due to their small particle size" [24].

(4.2) Parenteral Drug Delivery-

Nanocrystals can improve therapeutic efficacy via a variety of parenteral routes, including intravenous, subcutaneous, intramuscular, intraarticular, and intraperitoneal. An intravenous formulation of poorly soluble medicines requires numerous excipients such as surfactants and cosolvents in a traditional drug delivery system. However, these induce an increase in dose volume as well as a variety of side effects. Nanocrystals can be delivered intravenously with a lower dose, a faster onset of action, and maximum bioavailability due to their small particle size.

(4.3) Pulmonary Drug Delivery-

The size distribution of NCs can be used to control medication deposition in the lungs. The ultrasonic approach was used to prepare the aqueous nanosuspension for medication administration to the lungs. Poorly soluble medicines, such as beclomethasone dipropionate or budesonide, are critical for the local treatment of lung disorders. Nanocrystals have a tendency to attach the mucosal surface, resulting in a longer residence duration and increased medication absorption. NCs cause particle deposition in the pharynx and mouth, which has both local and systemic consequences. NCs are more evenly dispersed across the surface of the bronchi than microparticles. There are several examples of nanocrystal medication delivery to the lungs that are accessible.

(4.4) Ophthalmic Drug Delivery-

Due to eye physiological barriers and crucial pharmacokinetic surrounding settings, ocular administration is a difficult technology to implement. The most popular and noninvasive drug administration technique for the treatment of anterior segment eye disorders is topical application. Nanocrystals have advantages such as a long residence duration, which is necessary for the efficient treatment of most eye illnesses. It also has a poor tonicity, and their effectiveness is determined by medication intrinsic solubility in lachrymal fluids. As a result, the drug's bioavailability and ocular release are determined by its intrinsic rate of dissolution in lachrymal fluids.

(4.5) Targeted Drug Delivery-

Targeted drug delivery ensures that a significant amount of drug is accumulated in a

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specified treatment zone. Targeted drug delivery nanocrystals have a precise contact with a receptor in the targeted tissues. The four basic conditions for effective targeted medication delivery are: first retain, second evade, third target, and fourth release. I.v. drugs are sequestered and delivered by MPS cells. Compared to the solution counterpart, injected nanocrystals distribute more in MPS cell-rich tissues such the liver, spleen, and lung. On the surfaces of nanocrystals, targeted ligands and other functional groups can be added. Nanocrystals can be incorporated into various matrix structures and targeted for action in a specific tissue or organ utilizing this method.

V. CURRENT STATE OF DEVELOPMENT OF DRUGS USING THE NANOCRYSTAL TECHNOLOGY [25].

Sr. no	Tradename	Drug	Indication	Company
1	Rapamune®	Rapamycin	Immunesuppressive	Wyeth
2	Emend®	Aprepitant	Anti emetic	Merck
3	Tricor®	Fenofibrate	Hypercholesterolemia	Abbott
4	Megace ES®	Megestrol	Anti anorexic	Par Pharmaceutical Companies
5	Triglide®	Fenofibrate	Hypercholesterolemia	Sciele Pharma Inc.
6	Semapimod®	Guanylhydrazone	TNF-α inhibitor	Cytokine Pharmasciences
7	Paxceed®	Paclitaxel	Anti inflammatory	Angiotech
8	Theralux®	Thymectacin	Anti-cancer	Celmed
9	Nucryst®	Silver	Anti-bacterial	Nucryst Pharmaceuticals

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