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Nanocrystals-As Drug Delivery System

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ABSTRACT

Nanoparticles consists of organic and inorganic materials. Nanocrystals are aggregates of atoms that combine into a "cluster" and are pure drug crystals with sizes in the nanometer range stabilized or surrounded by a thin coating of surfactant. Todays nanocrystal formulation preparation method characterised as "bottom up" "top down" and "bottom up" spray drying methods. The majority of nanocrystal medicinal products are presently approved for oral ingestion and treatment of disorders other than cancer.

KEYWORDS: *Nanocrystalisation, bottom up, top down, medicinal products*

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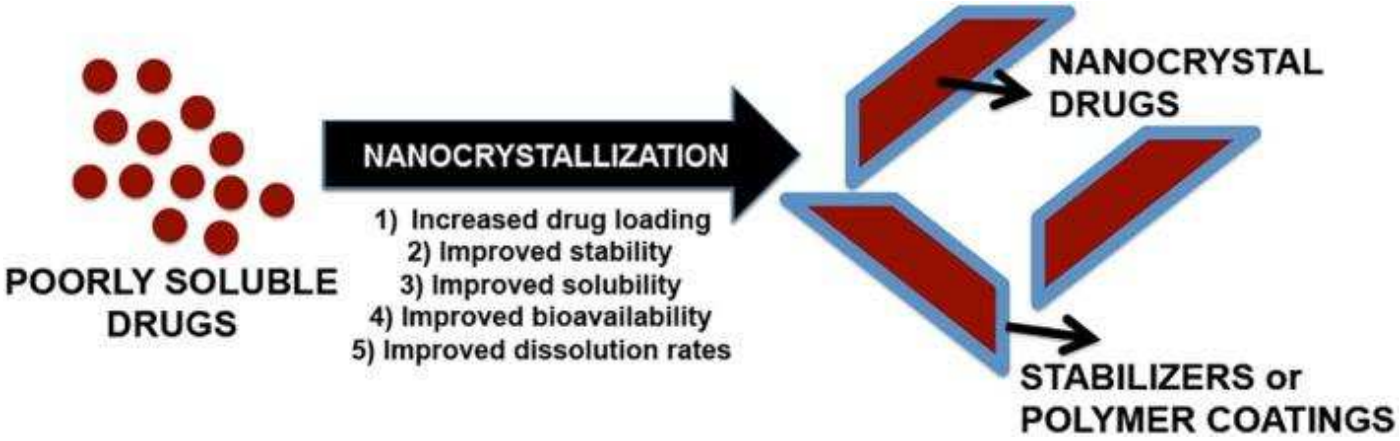
1. INTRODUCTION

Nanoparticles (NPs) consisting of organic and inorganic materials have been developed to bypass biological barriers and deliver medications for a range of applications over the years [1]. Water insoluble or hydrophobic medicines are difficult to achieve optimal absorption and, as a result, adequate efficacy [2]. According to a 2015 report, solubility issues affect 40% of on-the-market medications and 90% of drugs in the development pipeline [3]. According to other figures, intrinsic aqueous solubility concerns caused 40% of all potential medication candidates to be shelved [4]. As a result, a number of hydrophobic medicines that could be effective in therapies require clinically acceptable carriers [5].

Drug nanocrystals are defined as pure solid particles with a mean diameter of 1 m and a crystalline character for the purposes of this review article [6]. The platform provides a unique potential for delivering hydrophobic medicines (Figure1). 1). Its distinctiveness stems from the fact that nanocrystals are wholly made up of medicine or payload, removing the need for a carrier. Surfactants or stabilisers are also routinely utilised to keep crystalline dispersions stable in liquid medium [7].

Nanocrystallization enhances the physicochemical stability and bioavailability of poorly soluble medicines.



Because of the higher surface area to volume ratio and better dissolving rates (i.e., dissolution velocity) associated with nanosizing, nanocrystalline drug technology enhances the solubility of hydrophobic medicines. [8] Drug crystals are particularly well suited to the rehabilitation of previously ineffective BCS Class II and IV medicines (low solubility drugs). [9] The BCS classification system is an experimental approach for determining permeability and solubility under certain conditions. The medications are divided into four categories by the system. Class I medications have high solubility and permeability, Class II molecules have low solubility and high permeability, Class III pharmaceuticals have high solubility but low permeability, and Class IV drugs have low solubility but high permeability.

Nanocrystal medication formulations, also known as nanocrystal colloidal dispersions (NCDs), have been demonstrated to be stable in suspensions. The dispersions serve as a foundation for rapid scale-up and production of extremely stable and commercial products. Their synthesis and scale-up considerations have already been discussed in detail. [10,11] The utilisation of microfluidic-based platforms or the milling process, which is both flexible and programmable, are two often utilised synthesis strategies. [7],[12],[13], [14], [15], [16], [17]

The nanocrystal formulation technology has been used to save a number of hydrophobic medications. In the clinic, the medications were successfully developed and FDA approved for a variety of indications ranging from dental diseases to cancer. [14, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27,28] The approved formulations can be administered in a variety of ways, including oral, cutaneous, and parenteral, depending on the illness. This demonstrates how versatile a nanocrystal drug platform may be. Pharmacokinetic, biodistribution, and bioavailability data for organs implicated in nanocrystal-based delivery pathways have already been discussed extensively. [10, 13, 18, 24, 25, 29, 30, 31, 32, 33, 34] Lu et al. 2016 and 2017 reviews, in particular, look into the biodistribution pattern of nanocrystal medicines in the blood, heart, liver, spleen, lung, kidney, tumor, and thymus (i.e., the organs involved in clearance/circulation and host immune responses).[24, 35]

Several studies have been published that address the processes used to produce nanocrystal medicines, the types of stabilisers or surfactants utilised, and the physicochemical and biological characterization methods used. [10, 19, 36, 37] However, there is a significant translational gap between this extremely promising platform and clinical approval. From a translational standpoint, we address nanocrystal drug technology and its evolution in this review. Despite the platform's evident strengths, we discuss the lack of FDA-approved goods. We talk about the difficulties that come with bringing them to the doctor.

2. NANOCRYSTAL PREPARATION METHODS:

Several techniques of preparation are available. Today's nanocrystal formulation preparation methods can be characterised as "bottom up," "top down," "top down and bottom up," and "spray drying." The molecule is the starting point for "bottom up" technology; the active therapeutic material is dissolved by adding an organic solvent, and the solvent is then removed by precipitation. Different types of milling and homogenization techniques are used in "top down" technology to apply dispersion strategies. "Nanosizing" is a term for "top down" technology that is more popular than "bottom up" technology. To put it another way, it's a method for breaking down huge crystalline particles into small fragments. Both strategies are combined in "top down and bottom up" technology. Spray drying is another approach for making drug nanocrystals that is quicker and more practical than other methods.[40,41,42]

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.

2.1. BOTTOM UP TECHNOLOGY:

The principle of this approach is to dissolve the active drug material in an organic solvent before adding it to a non-solvent medium (miscible with the organic solvent). The nanocrystals are then precipitated in the presence of stabilisers. The primary benefit of the precipitation technique is that it is easy and inexpensive. Scaling up is also straightforward with this strategy. In order to create homogeneous nano crystals using this process, numerous parameters such as stirring rate, temperature, solvent/nonsolvent rate, drug concentration, viscosity, type of solvent, and stabiliser should be regulated [38].

2.2. PRECIPITATION METHODS:

The drug is dissolved in a solvent and then added to a nonsolvent, resulting in finely distributed drug nanocrystals precipitating. It's important to remember that when nanocrystals aren't allowed to develop to the micrometre range, they must be stabilised. Furthermore, the medication must be soluble in at least one solvent, which is a challenge for recently created medicines that are insoluble in both aqueous and organic mediums. This technology has yet to be applied to a product due to some of the aforementioned issues. At a specified temperature, a carotenoid solution with a surfactant in digestible oil is mixed with a suitable solvent. A protective colloid is used to obtain the solution. This results in a two-phase O/W system. The colloid-stabilized carotenoid settles in the oily phase. X-ray examination of the carotenoid after lyophilization reveals that roughly 90% of it is amorphous [39].

2.3. TOP DOWN AND BOTTOM UP TECHNOLOGY:

Both strategies are employed in "top down and bottom up" technologies. Nano-Edge is a product made possible by combining these technologies. The formulation approach for poorly water-soluble pharmaceuticals was described using nano-edge technology. It's a good option for active compounds with high melting temperatures and noctanol-water partition coefficients. Direct homogenization, micro precipitation, and lipid emulsions are used. The medication is first dissolved in a water-miscible solvent to generate a solution in micro precipitation. The solution is then mixed with a second solvent to generate a pre suspension, after which energy is applied to form particles with an average effective particle size of 400 nm to 2 nm.

2.4. SPRAY DRYING:

Spray drying is one of the procedures for preparing nanocrystals. This technique is commonly used to dry liquids 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 formed. Spraying is done with an atomizer that spins quickly and scatters the solution due to the centrifugal force. A peristaltic pump delivers the solution to the inner tube at a set flow rate, while nitrogen or air at a constant pressure is delivered to the outer tube. A nozzle is used to spray the product. Because spraying reduces the size of solution droplets, the surface area of the drying matter increases, resulting in rapid drying. The solution's concentration, viscosity, temperature, and spray rate can all be tweaked, as well as particle size, fluidity, and drying speed. This approach enhanced the solubility rate and bioavailability of numerous medicines, including hydrocortisone and COX-2 Inhibitor (BMS-347070).

3. NANOCRYSTAL-DRUG PRODUCTS:

Nanocrystals have sparked a lot of research and development because of their high drug loading efficiency, consistent dissolution rates, improved structural stability, and longer circulation durations. Several medications are already on the market, and clinical trials are underway for a number of other formulations.

3.1. NANOCRYSTAL MEDICINAL PRODUCTS FABRICATION TECHNIQUES:

A sonicator, homogenizer, mortar and pestle, or jet mill is used to turn raw or surfactant-dispersed drug particles into micronized suspensions during HPH. [43,44,45,46,47] After passing through a narrow gap, the suspensions

are subjected to a sequence of collisions, intense cavitation, and significant shear forces. As a result of the pressure changes, it begins to boil. Precipitation is the most typical strategy for a bottom-up approach. Nanosuspensions are created by mixing totally dissolved tiny molecules with their antisolvent. Nucleation and crystal formation are the two steps involved. An acid–base neutralisation step is one of the other techniques. Nanosuspensions are made by dissolving a medication in an acidorganic solvent mix and progressively adding a base until the solution is neutralised. Techniques such as microfluidic nanoprecipitation, spray drying, electros praying, and aerosol flow reactor have also been used to make nanosuspensions. [49,50,51,52,53] [Table1] summarises the benefits and drawbacks of both topdown and bottomup techniques.

Table1 TOP -DOWN VERSUS BOTTOM UP APPROACHES FOR NANOCRYSTALS DRUG PRODUCTS:

	Technique	Merits	Limitations
Top-down approaches	Media milling (MM)	1. Works for drugs that are insoluble in both aqueous and non-aqueous solvent. 2. no organic solvents are used 3. ease of scale-up 4. minimal batch to batch variation 5. narrow size distribution of particles 6. high drug loading efficiency	1. Costly manufacturing process 2. high energy requirements with long durations for milling 3. could destabilize the drugs due to high shear forces and temperature 4. risks for contamination from the dispersion media 5. unwanted drug loss
	High-pressure homogenization (HPH)	- Same as MM -	1. Particles need to be micronized and form suspensions 2. risk of contamination including machine debris 3. high energy requirements
Bottom-up approach	Precipitation	1. Simple and less expensive 2. minimal energy requirements 3. ease of scale-up 4. possible non-stop production	1. Extensive optimization required selecting solvent/antisolvent 2. possible growth of particles with time 3. inadequate purification process or removal of toxic solvents

3.2. NANOCRYSTAL DRUGS PRODUCTS IN THE MARKET:

Since 1995, the FDA has approved 50 nanodrugs for diverse reasons, most of which are based on liposomes, polymers, and nanocrystals. [54,55] Nanocrystallization is a good approach to create and produce medications that aren't very soluble. The technology's economic value is boosted even further by the short time it takes to get clinical approval. While liposomes took nearly 25 years to market, Emend® took only ten years. Emend originally filed a patent application in 1990, and the product was released in 2000. [56] In comparison to other nanosized platforms, a substantial number of nanocrystal medicinal products have been successfully produced and released in a short period of time. [56]

In the year 2000, Wyeth Pharmaceuticals (Madison, NJ) developed Rapamune®, a poorly soluble immunosuppressant called Sirolimus (SRL), as the first marketed nanocrystal medication. Rapamune was developed using pearl mill technology, and its oral bioavailability was shown to be 21% higher than SRL in its standard oral solution form. Merck released Emend (Aprepitant) in 2003, which was followed by the launch of Emend (Aprepitant) in 2004. (Winehouse Station, NJ). Aprepitant, a weakly water soluble antiemetic drug that can only be absorbed in the upper gastrointestinal tract and has a small absorption window, was used to create Emend. Aprepitant was nanoionized using pearl mill technology, which enhanced its oral bioavailability by making it more water soluble Tricor® was developed utilising the pearl mill technology process from fenofibrate, a lipophilic medicine for hypercholesterolemia, and introduced by Abbott Laboratories in 2003. Fenofibrate was made into nanocrystals, which boosted its adhesiveness to the gut wall and improved its oral bioavailability by 9%, regardless of whether it was fed or fasted. This allowed patients to have a more straightforward and flexible dosing plan. Triglide®, a nanocrystal medicine developed from fenofibrate that was introduced by Skyepharma in 2005, is another fenofibrate-derived nanocrystal drug. Triglide nanocrystals were made using the HPH technique and have comparable properties as Tricor. Triglide boosted gut wall adhesiveness and improved bioavailability regardless of whether the patient was fed or fasted. Sciele Pharma

Inc. now markets Triglide (Atlanta, GA). Megace ES®, a nanocrystal product, was introduced in 2005 by Par Pharmaceutical Companies, Inc. (Spring Valley, NY). Using the pearl mill method, Megace ES was manufactured into nanocrystals from megestrol acetate, an appetite stimulant. When compared to the highly viscous megestrol acetate oral suspension, this improved its dissolving rate and reduced the single dose volume by four times, boosting oral bioavailability and patient compliance. [Table 2] lists other approved nanocrystal drug items, and media milling is the most widely acknowledged process for producing the majority of the marketed medicines.

Table 2 NANOCRYSTAL DRUGS PRODUCTS IN THE MARKET:

Trade name	Company	Drug	Indication	Technology	Delivery route	Approval year
Rapamune	Wyeth	Rapamycin/sirolimus	Immunosuppressive	Coprecipitation	Oral	2000
Emend	Merck	Aprepitant	Anti-emetic	Media milling	Oral	2003
Tricor	Abbott	Fenofibrate	Hypercholesterolemia	Media milling	Oral	2004
Triglide	Skye Pharma	Fenofibrate	Hypercholesterolemia	High pressure homogenization	Oral	2005
Megace® ES	Par Pharma	Megestrol acetate	Appetite stimulant	Media milling	Oral	2005
Invega Sustenna®	Johnson & Johnson	Paliperidone palmitate	Antidepressant	High pressure homogenization	Parenteral	2009
Cesamet®	Lilly	Nabilone	Anti-emetic	Coprecipitation	Oral	2009
Avinza®	King Pharma	Morphine sulfate	Anti-chronic pain	Media milling	Oral	2002
Naprelan ®	Wyeth	Naproxen sodium	Anti-inflammation	Media milling	Oral	2006
Ritalin LA®	Novartis	Methylphenidate hydrochloride	Anti-psychotic	Media milling	Oral	2002

3.3. CLINICAL TRIALS OF NANOCRYSTAL MEDICINAL PRODUCTS:

The majority of nanocrystal medicinal products are presently approved for oral ingestion and treatment of disorders other than cancer, as shown in [Table2]. Oral administration has a huge market, and the path to commercialization is more easier than injectables. The regulatory approval process for nanocrystal drug products is simplified because the product is mostly made up of the medicine and can include GRAS authorised stabilisers and excipients. As a result of the practicality of quick development and commercialization, various nanocrystal therapeutic items are currently being tested in clinical studies, as shown in [Table3]. During a Phase I research in cancer patients, Semapimod nanocrystals from Cytokine Pharamsciences (CPSI) were discovered to operate as an immunomodulator, reducing the generation of TNF, a proinflammatory cytokine involved in inflammation-associated carcinogenesis. [57] During an early clinical trial, CPSI discovered that the medicine was helpful in treating psoriasis and moderate-to-severe Crohn's disease. PAXCEEDTM, a nanocrystal medication developed by Angiotech Pharmaceuticals, Inc., is currently in clinical testing. [58] PAXCEED is a cremophor EL-free systemic formulation that is made from paclitaxel. This could help individuals who are being treated for cancer or chronic inflammation to have less hypersensitivity. Celmed BioSciences Inc. (Saint-Laurent, QC) has developed TheraluxTM, a photodynamic therapy-based treatment system based on thymectacin, which is poorly soluble and has low bioavailability. [59] It's currently being tested in autoimmune illnesses, non-lymphoma, Hodgkin's colon cancer, and graft versus host disease prevention. Nucryst Pharmaceuticals (Wakefield, MA) has created a cream formulation based on NPI 32101, a patented material predominantly made up of silver nanocrystals. [60,61] The medication has anti-inflammatory and antibacterial effects that were promising. [62] For atopic dermatitis, NPI 32101 is now in Phase II clinical studies. [63] 2Methoxyestradiol (2ME2), a natural metabolite of estradiol, was used to create Panzem® NCDs (EntreMed, Inc.). During preclinical testing, 2ME2 demonstrated promising antiproliferative and antiangiogenic capabilities. Following that, Entremed decided to evaluate Panzem's activity against ovarian cancer and other solid carcinomas. However, it did not go past Phase II, and Panzem's clinical research was halted. [64]

Table 3

Trade name	Company	Drug	Indication	Technology	Delivery route	Clinical status
Semapimod	Cytokine Phamasciences	Guanylhydrazone	TNF-α Inhibitor	Self-developed	Intravenous	II
Paxceed®	Angiotech	Paclitaxel	Anti-inflammatory	Unknown	Intravenous	III
Theralux	Celmed	Themectacin	Autoimmune diseases and cancer	Media milling	Intravenous	II
Nucryst®	Nucryst Pharmaceuticals	Silver	Atopic dermatitis	Self-developed	Topical	II
PanzemNCD	EntreMed	2-methoxy estradiol	Ovarian cancer	Media milling	Oral	II

3.4. CHALLENGES AND CRITERIA IN THE CLINICAL DEVELOPMENT OF NANOCRYSTAL-DRUG PRODUCTS:

The development of nanocrystal drug technology has progressed dramatically during the last two decades. The bulk of the active pharmaceutical ingredients (API) utilised in these formulations are insoluble in water. As a result, the medications' systemic bioavailability after administration is affected, resulting in difficult dosing regimes for patients. Nanoionization of such APIs can lead to smaller particles, a higher surface/volume ratio, and a faster rate of dissolution. As a result, when compared to its original composition, this could increase dosage proportionality, linear pharmacokinetics, and bioavailability. Physicians might then estimate therapeutic response and tailor dose regimes to the specific needs of each patient. During scale-up and development, however, concerns with quality, chemistry, manufacturing, and controls, or bioequivalence (BE), of nanocrystal medicinal products still exist. This could stymie the development of promising nanocrystal therapeutic formulations for a range of diseases in the clinic.

Determining the best settings for assessing in vitro dissolution rates of freshly designed goods is one such difficulty. The drug molecules are released from the crystal surface into the surrounding dissolution media to create a saturated layer close to its surface, and then the released molecules diffuse through the solvent from a region of high concentration (i.e., the saturated layer) to a region of low concentration. During the development and manufacture of a newly designed nanocrystal medicinal product, determining the dissolution rate is critical. It would meet all of the requirements for international regulatory standards while also ensuring safety, efficacy, and quality Dissolution studies must be performed in vivo or in settings that imitate in vivo, depending on the administration method. If given orally, for example, the medications must be released from the crystal, absorbed by the GI system, and circulated in the bloodstream before reaching the site of action. The study design should account for the difficult gastric conditions, such as the acidic pH (1–3), continual churning, the pH (5–7) of the intestinal compartment, and so on.

The Noyes–Whitney equation is frequently used to describe the rate of medication dissolution at a given period. [65]

$$Dx/dt = A.D/\partial.Cs - (Xd/V)$$

Dx/dt is the dissolution rate, A is the dissolving particle's surface area, D is the diffusion rate constant, is the thickness of the stagnant layer surrounding the particle, Cs is the drug's saturation solubility, X d is the amount of drug dissolved at time t, and V is the volume of the dissolution media.

As a result, if the dissolution media enhances drug solubility, it should also increase the rate at which the crystal dissolves. As a result, it's critical to use in vitro conditions that closely resemble the physiological milieu. Dissolution procedures now in use, such as the paddle method paired with UV spectroscopy or HPLC, do not accurately imitate physiological circumstances. As a result, there is a lot of variation between in vitro dissolution and in vivo bioavailability data. The use of microfluidic coculture technologies that account for physiological concerns could make the transition to the clinic go more smoothly. [66],[67],[68] It would be beneficial to evaluate the product's quality and predict its in-vivo performance. As a result, the number of BE studies conducted in people during clinical development, scale-up, and post-approval adjustments will be reduced.

Other obstacles encountered during product development include: (a) drug substance control, (b) drug product control, (c) manufacturing process, and

(d) drug substance/drug product stability. Drug material is referred to as the API without excipients depending on purity and achieves the final therapeutic effect. The effect is determined by physical characteristics like size and crystallinity. This could have an impact on the production process and the final product's quality. Because particle size and distribution are influenced by the dispersion media and stabilisers used during the formulation process, values are expressed as particle size distributions (D values). During submissions, the D values represent the midpoint and range of values. Specifications are expressed using histograms as intensity weighted harmonic mean (Zaverage) and polydispersity index where appropriate. Another issue would be determining the best method for validating particle size. To maintain consistency, determine particle size and dispersion using at least two analytical approaches that complement each other. Because the pH of the dispersion media commonly affects nanocrystal size and stability, it may be taken into account. Changes in crystallinity, such as amorphous or polymorphic variations, may have an impact on solubility, stability, and bioavailability. As a result, it's critical to ensure that the finished product's crystalline structure is monitored and managed throughout its manufacturing and shelf life. [69] [70] [71][72][73] [74] [75][76]

The prototype or marketed dosage form of a drug ingredient prepared with excipients is referred to as a drug product. Its control refers to the aspects that influence the final product's quality and in-vivo performance. Changes in viscosity, dissolving rate, specific gravity, content homogeneity, and redispers ability can all effect this. The presence of contaminants created during production also has an impact on the variables. As a result, assays that assess purity and continuously monitor degradation products created during manufacturing or shelf life of the finished product must be given careful consideration.

Determining the most appropriate tests or controls to monitor particle size distribution, agglomeration, and the presence of pollutants at various stages of the manufacturing process are key factors. As a result, it's critical to keep track of any contaminants that arise during the process. [78],[79] Impurities in a topdown technique, such as wet milling, are determined by the milling media utilised, the milling material that comes into contact with the medication, the milling mechanism, and the number of milling cycles used. Other elements that may affect the process and particle size distribution include product and chiller temperature as a function of time, drive motor speed, shape, aspect ratio, viscosity of product dispersion, and so on. [77] [78][79] In the case of a bottom-up approach, care should be taken to ensure that (a) uniform dispersion of the drug is maintained and agglomeration is avoided while slowly adding the drug into the melt, (b) optimal viscosity for the molten material is maintained, (c) consistency is maintained during sampling and the solidification/cooling procedure, and (d) solvent residues and other impurities in the drug substance/product are tracked and isolated on a regular basis. Deviations in any of the foregoing steps could have a major influence on product quality and performance in vivo.

Because the finished product's crystallinity can have a substantial impact on its quality and in vivo performance, it's critical to maintain structural stability after manufacture and throughout its shelf life. Techniques like X-ray powder diffraction, differential scanning calorimetry, and spectroscopic methods, among others, can be used to investigate and compare the structure of the starting molecule with the final product and at the end of its shelf life, as previously indicated. Because particles tend to clump due to sedimentation, redispersion, or caking, and other factors, additional research on short or long term stability, as well as dosage form, may be designed.

CONCLUSION:

Nanocrystals can be adopted by all poorly soluble drugs to defeat their solubility and bioavailability issues. The reduction in particle size to nanometer range adds to the enhanced particle surface, curvature, saturation solubility, dissolution velocity and further reasonable bioavailability. Nanosuspensions are specific and economically conceivable way to deal with tackle the issues of hydrophobic drug, for example, poor solubility and poor bioavailability. For excessive large scale nanosuspensions production, high pressure homogenization and media milling technology have been viably used. Striking characteristics, similar to progress of dissolution velocity, enhanced saturation solubility, upgraded bioadhesivity, versatility in surface modification, and burden less postproduction processing have expanded the uses of nanosuspensions for different routes of administration.

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