International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Nano-crystals a comprehensive review on formulation and application perspectives

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Received - 20-01-2023**, Revised** - 17-04-2023, **Accepted** - 12-05-2023 **(DD-MM-YYYY)**

Refer This Article
Mishra Rakesh, DhadwadSagar, AherAkash, DhokalePrajakta, 2023. Nanocrystals a comprehensive review on formulation and application perspectives. Journal of medical pharmaceutical and allied sciences, V 12 - I 3, Pages - 5806 – 5816.
Doi: https://doi.org/10.55522/jmpas.V12I3.4798.

ABSTRACT

A majority of recently invented medications have been discovered to be poorly water soluble and causes delays in the formulation and development of dosage forms. Solubility has been a major problem for BCS classes II and IV. As a result, nanotechnology may be useful in resolving the solubility problem. This review will cover Nanocrystals, as well as the numerous methodologies employed in their formulation and their application. Nanocrystals are nanometre-sized drug particles of a poorly-water-soluble compound. They are distinct from polymeric nanoparticles in that they are entirely made up of the drug. Nanocrystals can be implemented to increase the rate of dissolution and saturation solubility of active pharmaceutical ingredients. Milling, high-pressure homogenization, precipitation, and combination methods such as Nanoedge andSmartCrystal, are among the approaches available for its formulation. The transition of nanocrystals into final formulations, as well as future nanocrystal trends, are also discussed.

Keywords: Nanotechnology, Nanocrystals, Techniques of production of nanocrystals, Poorly water-soluble drugs, Bioavailability enhancement.

INTRODUCTION

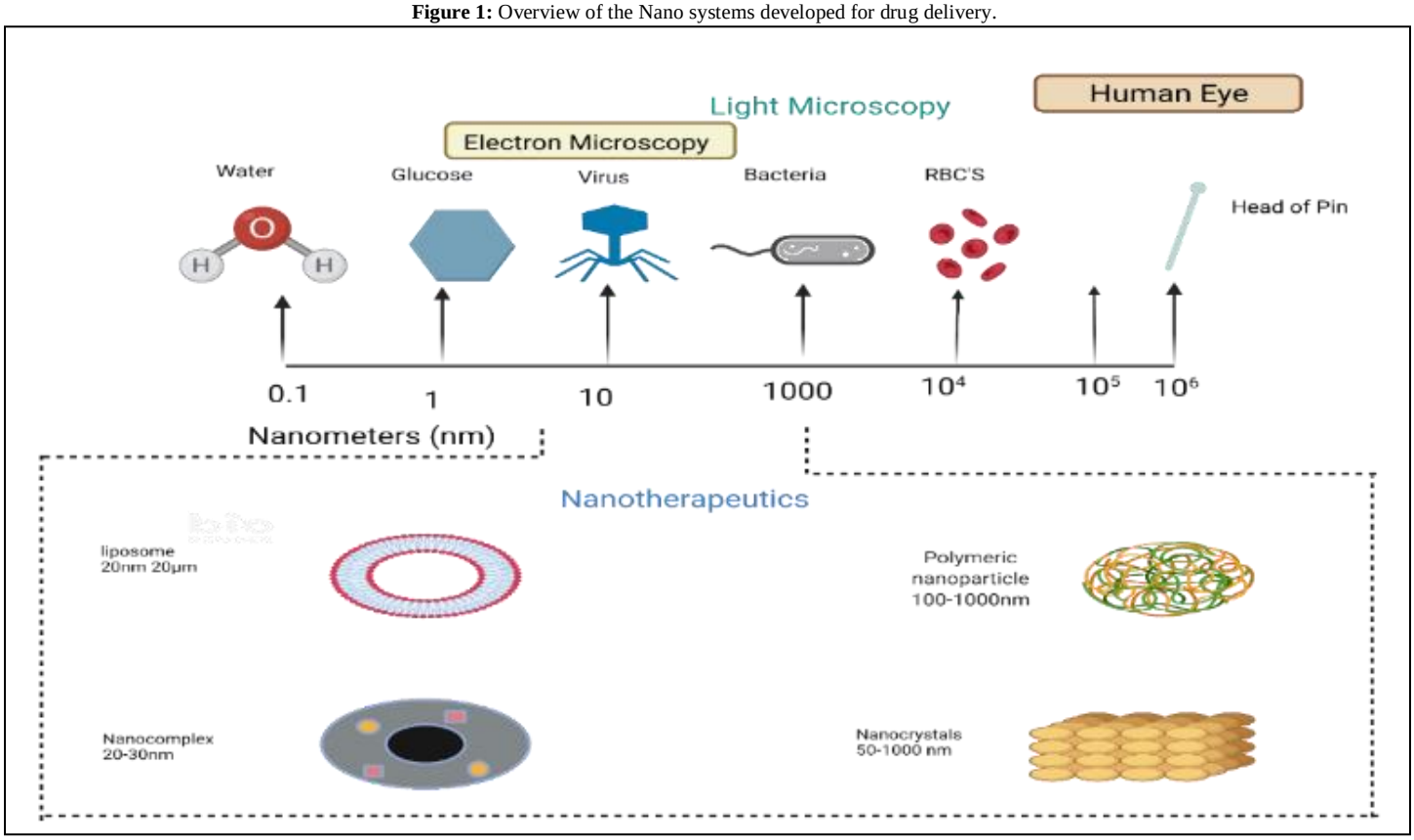
The successful integration of most current or future pharmaceuticals into the human body has been a challenge for formulation researchers [1]. A quarter of all novel pharmaceutical agents are predicted to be water insoluble, and challenging to make formulations. A formulation scientist's main goal is to create a suitable delivery system with a greater drug dissolution rate that can aid in increasing bioavailability and limiting unwanted effects [2]. Solubility, dissolution, and gastrointestinal permeability are crucial aspects that limit the rate and amount of medication absorption as well as its bioavailability [3].

Limited and extremely varying bioavailability seems to be a widespread major issue with regular formulations of inadequately water-soluble medications. Physical and chemical modification strategies, to increase solubility are lessening particle size (nanonization), developing polymorphs (solvates), Complexation / Solubilization (utilizing surfactants or cyclodextrins, conjugation to dendrimers, co-solvent inclusions), formation of drug dispersions in carriers (eutectic mixtures, non-molecular solid dispersions, solid solutions).However, it appears that a shift from micronization to nanonization is required to further improve the drug dissolving rate and consequently bioavailability. This involves nanotechnology-based strategies and novel approaches to all nanostructure-related physicochemical and stability issues [4]. The nano systems formulated for various drug delivery systems are shown in Figure.1.

The emergence of nano-crystals aided in mitigating the concern of inadequately soluble pharmaceuticals, particularly for oral or parenteral drug delivery, and contributed to the development of several marketed medications [5]. Nano-crystals have been termed as a sub-micron colloidal dispersion of stabilizers and Active Pharmaceutical Ingredients. Drug nano-crystals are crystals with nanoscale size, confirming that they are crystalline nanoparticles. Drug nano-crystals differ from polymeric nanoparticles in that they are composed wholly of the drug, as opposed to polymeric

nanoparticles that comprise a carrier component. When drug nanocrystals are disseminated in liquid media, they form "Nanosuspensions'. Surfactants or polymeric stabilizers must be utilized to stabilize scattered particles in general. Based upon the production technique, the conversion of drug microcrystals into drug nanoparticles may result in either a crystalline or perhaps an amorphous output, particularly if precipitation is used. It has the potential to increase the solubilization of weakly soluble drugs by lowering drug particle size. Some of the stabilizers in the nanocrystal formulation had a solubilizing effect, which may improve medication absorption in vivo much further. Consequently, nanocrystals with high drug loading and dispersion could well be employed at a lesser dose for oral administration, yielding improved patient satisfaction and lower risk [6].

Figure 1: Overview of the Nano systems developed for drug delivery.



Advantages

These could be administered using any route.

- Decreased skin irritation whether administered subcutaneously or intramuscularly.
- The IV route of administration enables rapid dissolution as well as tissue targeting. When nanosuspension is taken orally, it has a faster onset, a lower fed/fasted ratio, and higher bioavailability.
- As a result of the obvious reduction in particle size, the absorption from the absorption window can be enhanced.
- Drugs having greater log P-value could be converted to nano crystals for promoting bioavailability.

Nano crystals could be included in tablets, pellets, hydrogels, even suppositories enabling different delivery methods. By enhancing the amorphous fraction of the particles, the crystalline structure may be altered, resulting in improved solubility.

Surface tailoring enabling site-specific delivery is indeed an option.

Physical as well as chemical stability over time (owing to the lack of Ostwald ripening)[7].

Disadvantages

- Physical stability, sedimentation, as well as compaction are all potential issues.
- Due to the bulkiness of products, they must be handled and transported with utmost caution.
- It is challenging to achieve a uniform and correct dosing [8].

Properties of nano crystals

Enhanced dissolution velocity because of increased surface area

Decreasing size results in enhanced surface area and dissolution velocity, as per the Noyes-Whitney equation. As a result, where dissolving velocity is the rate-limiting step, micronization is an effective approach for enhancing bioavailability. Micronization to nanonization increases particle surface area, which in turn raises the dissolving velocity. Poor dissolution velocity is usually associated with poor saturation solubility. Noyes and Whitney Equation:

$$\frac{dc}{dt} = \frac{DA}{h}(Cs - Cx)$$

Where dc/dt is the dissolving velocity, D is the diffusion coefficient, A is the drug particle's surface, h is the diffusion layer's thickness, Cs is the drug's saturation solubility, and Cx is the drug's concentration

in the surrounding liquid at time[7].

Increase in saturation solubility

When nanosized substances are compared to micrometre particles, their saturation solubility increases, and their kinetic saturation solubility increases as well. This is based on the Kelvin equation, which specifies vapor pressure as a function of liquid droplet curvature in a gas phase. Nano crystals produce a supersaturated solution as compared to micrometre crystals [9].

Increased Adhesiveness

Nano crystals are naturally adhesive to biological mucosa and also gastrointestinal mucosa [10]. The development of hydrogen bonds and van der Waals bonds among both the particle surfaces as well as mucus leads to the binding of nano crystals, in suspension or those formed followed by the disintegration of a solid dosage form, to the gastrointestinal mucosa. The longer retention of nano crystals results in a larger gradient of concentration from across GIT, which increases medication absorption as well as thus bioavailability [11].

Improved Stability

Nanocrystal being a simple formulation mainly composing of only drug and stabilizer (in nanosuspension it may contain a suitable dispersion medium), there are very less chances of chemical reaction in Drug Nano crystal while comparing with other novel drug delivery systems that may include many excipients to form stable *final formulation.*

The Versatility of Final Dosage Form

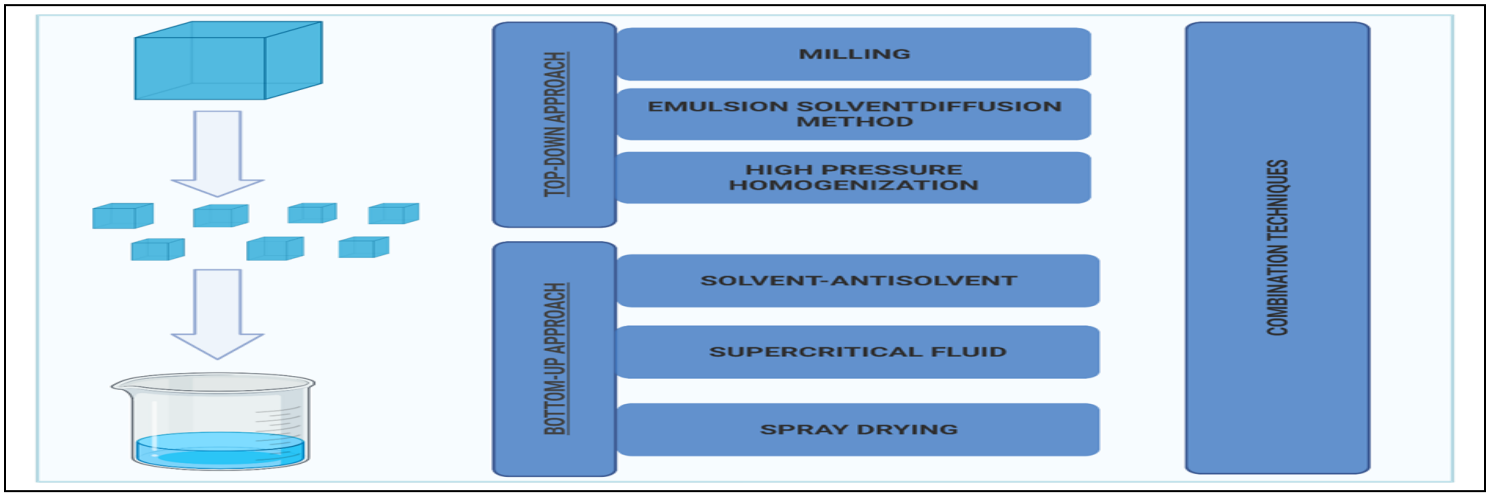
NCs provide a flexibility in adjusting surface properties and regulating the size with such an easy and efficient way of post-production that enables them for transferring them in various dosage forms like tablets, pellets, capsules, dry suspension and gels [10].

Nano crystal Manufacturing Methodologies

Bottom-up technology

This approach relies on precipitation, which is attained by solubilizing the drug in a solvent and thereafter introducing the solution to a non-solvent, resulting in the tiny microscopic particle precipitating depicted in figure 2.

Figure 2: Schematic representation of the main methodologies for the Manufacturing of drug nano crystals, using top-down and bottom-up approaches**.**



Anti-solvent precipitation

This is a mechanism for producing nanoscale particles by increasing particle size from molecule to nanoscale. Simple laboratory apparatus is used in this technique to prepare nanosuspension which is further freeze-dried to obtain nano crystals. The drug is first dissolved in a suitable organic solvent and afterwards blended with miscible anti-solvent. The drug's solubility in water is poor, therefore it precipitates. Surfactants must be used to control the growth of crystals throughout the precipitation process in order to prevent the formation of microparticles. However, at least one solvent must be soluble in the drug, and the solvent must be in non- solvent. It also doesn't apply to medications that are weakly soluble in both aqueous and non-aqueous systems [11,12].

Supercritical fluids

The ability to quickly remove the SCF as well as a solvent without the requirement for a lengthy drying stage is a significant benefit of the SCF method. SCF technique takes advantage of supercritical fluid's distinctive physical qualities, such as lower density and viscosity, as well as high diffusivity, to achieve quick micro-mixing for precipitation [13]. The RESS (rapid expansion of the supercritical solution procedure) includes a nozzle expanding a drug solution in supercritical fluid, causing the supercritical fluid's solvent power to be lost as well as the drug to precipitate as minute particles. Drawbacks of the aforementioned methodology include the use of hazardous solvents as well as greater ratios of surfactants and stabilizers when particularly in comparison to numerous different methods, particle nucleation overgrowth because of temporarily raised super saturation, which also might very well lead to the production of an amorphous form or perhaps another unintended polymorph [14].

Spray-drying

Spray drying is one method of preparing nano crystals. A drug solution (aqueous or non-aqueous) gets atomized into small droplets and evaporated in a hot airflow current to generate dried

particles in spray drying [13,15] .

Precipitation Assisted by Acid-Base Method

In the carbon dioxide-assisted precipitation method, the medication is typically dissolved in a weak acid solution as the acid phase and a weak base in a solution containing stabiliser as the base phase. The acid phase is introduced to the base phase to produce carbon dioxide, then the drug nano crystals are precipitated by vapor effervescence [16]. This approach is more environmentally friendly because it does not involve the addition of organic solvents. It only applies to insoluble medications whose solubility is pH-dependent and acid-base stable. Tacrolimus nano crystal suspensions were made using this technique by Wang et al. [17]

High Gravity Controlled Precipitation

High gravity controlled precipitation (HGCP) is a modification of precipitation method in which gravity is employed that produces more homogeneous and smaller drug nano crystals. [18] The three most important variables that affect particle size are reactant concentration, rotating speed, and volumetric flow rate. This method allows for continuous mixing and reacting of the drug suspension in the apparatus which leads to oversaturation of the feed stream at the turbulent edge during mixing resulting in continuous nucleation, thus limiting the industrial application of this method. Salbutamol sulphate [19] and sorafenib have both been successfully prepared on a laboratory scale using this technology.

Emulsion Polymerization Method

An O/W emulsion is created by dissolving API in volatile organic solvents or partially mixed solvents with water that have been used as the dispersion phase which is emulsified using stabilizers. To obtain drug nano crystals, the emulsions are then evaporated, mixed, and extracted. The quality of the final product is significantly influenced by elements like the emulsifier, stirring rate, evaporation rate, temperature gradient, and pH value. This method cannot be used for large-scale pilot production since it needs the aid of homogenization or ultrasonic and hence is used on laboratory scale only. Florfenicol nano crystals were developed using this method.

Top-down Technology

Large crystals of the micrometre range are by diminution to produce crystals of nano range.

Media Milling (Nano crystals or Nano systems)

Bead Milling

`Liversidge et al. developed this patent-protected technology (1992). Nanosuspensions are prepared to utilize high-shear media mills and perhaps pearl mills in bead milling. A media mill is made up of three parts: a milling chamber, a milling shaft, and a recirculation chamber that all rotate at a high shear rate[20]. The milling media (e.g., milling beads), particulate material, stabilizer, along an appropriate solvent or solvent mixture are all fed into the milling chamber during wet media milling. Strong, dense materials like yttrium-stabilized zirconium oxide, stainless steel, glass alumina, titanium, or polymers including strongly cross-linked polystyrene as well as methacrylate are used to make milling beads. Beads can be anything between 0.1 and 20 mm in size [21] . The milling technique is performed at specific temperatures. The energy input needed to fracture the micro particulate drug into nanosized particles is provided by the high energies and shear pressures created by the milling media impaction on the drug [20].

Dry co-grind

`Wet–grinding procedures include high-pressure homogenization of nanosuspensions as well as the media milling with a pearl-ball mill. Dry co-grinding is a simple and cost-effective process that does not require the utilization of organic solvents. This method can produce a stable amorphous solid by reducing particle sizes to submicron levels [22]. Cogrinding employing β-CD with a greater water percentage can be an efficient way to produce ultrafine submicron drug particles [23].

High-pressure homogenization

Homogenization in Aqueous media (Dissocubes)

R.H. Muller created this method in 1999, and DDS Gmbh obtained the initial patent, which was later transferred to Skyp Pharmaceuticals. The APV Micron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany) and piston-gap homogenizers are commonly used homogenizers. The instrument may be used at pressure ranges between 100 to 1500 bars (2800–21300 psi) and 2000 bars with a 40 ml volume capacity (for laboratory scale). Presuspension of the micronized medication in a surfactant solution with a high-speed stirrer is required in manufacturing nanosuspension. This leads to the boiling of water at ambient temperature, generating gas bubbles that implode as the suspension leaves the gap (a process called cavitation) and normal air pressure is restored. Temperature, the number of homogenization cycles, the homogenizer's power density, and the homogenization pressure affects the drug nanocrystals' size. Pre-processing, such as drug micronization and high-priced equipment, raises the total cost of the dosage form. This approach was used to make nanosuspensions of pharmaceuticals such as Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine, and Dexamethasone [24].

Homogenization in Non-Aqueous Media (Nanopure)

Using Nanopure technology, homogenization can be done in either a non-aqueous or a low-water phase. Homogenization was observed to be equivalent or perhaps better effective at reduced temperatures, well under the freezing point of water, in contradiction to more severe cavitation at higher temperatures. The turbulent flow's shear forces are sufficient to fracture the drug microparticles. At lower temperatures, certain compounds become

more brittle (e.g., polymers). When pharmaceuticals are homogenized in a non-aqueous or water-reduced medium at low temperatures, their chemical stability is not compromised [25].

Nanojet Technology

Opposite stream technology is another name for nano jet technology. Because of strong shear forces generated throughout the operation, a stream of suspension in two or more separated sections was driven with high pressure and forced to colloid with one another. As a result of the significant shear forces generated throughout the procedure, particle size was reduced [26].

Emulsion solvent diffusion method

This type of emulsion can also be used to make nanosuspensions. It is used to make pharmaceuticals which do not dissolve in volatile organic solvents or are sparingly soluble in water. There are two ways to perform an Emulsion solvent diffusion method. In the first type, organic solvents or a combination of organic solvents and drugs and water phase with adequate surfactants is made. Then the organic phase is evaporated at a lower pressure. Lastly, a nanosuspension was produced, which was stabilized with the use of appropriate surfactants & stabilizers. In the second type, the dispersed phase is formed with partly miscible solvents [27].

Laser Ablation

The solid target is exposed to laser light during laser ablation, and the material that is expelled condenses into nanoparticles in the surrounding liquid. Then, stirred suspensions of micro particles are broken into nanoparticles by laser-mediated fragmentation [28]. It is divided into nanosecond, picosecond, and femtosecond laser irradiation, among which more nanoscale particles can be produced. The intensity of the laser, the speed of the scanner, the characteristics of the suspension, and other factors all have an impact on particle size. Although there are no organic solvents used in this process, a small amount of the drug could experience oxidative degradation and crystal state changes as a result of using too much power. Paclitaxel, megestrol acetate, and curcumin nanosuspensions were prepared using this method [29].

Ultrasound

Ultrasound method uses vibration of acoustic waves to reduce particle size of drug. It has been shown to enhance nucleation by creating acoustic cavitation in solution and rapidly dispersing the drug solution [30]. It is frequently coupled with other procedures since it is simple to use in the lab and is highly reproducible. The key processes affected include mixing, nucleation, growth, and agglomeration. The length of the horn, the horn immersion depth, and the cavitation depth are all factors that affect the nano crystal's size [31].

Combination technology: (Patented Technologies of Nanosuspension):

Nanoedge™

Nanoedge is based on the same principles as precipitation as well as homogenization. Within a shorter amount of time, a composite of these processes results in lower particle size and good stability. The precipitated dispersion is homogenized further, resulting in smaller particles and also the avoidance of crystal formation. An evaporation step can sometimes be implemented by changing the starting material that is solvent-free, accompanied by high homogenization, enabling the successful manufacture of Nanosuspensions employing the Nano edge technology [32].

Smart Crystal® Technology

Smart Crystals as the second generation of the drug nanocrystals differ in their physicochemical properties [33]. The smart crystal technology is a "toolbox" incorporating multiple nanocrystal development technologies that can be combined. Further, using the smart crystal toolbox, process variations such as homogenization using water-ethanol mixtures or perhaps the addition of chemicals that promote crystal diminution can be selected [34]. The H42 technique combines spray drying with high-pressure homogenization. The H96 method combines lyophilization and HPH [33].

Other methods

Solvent evaporation

The solvent evaporation method is used to create polymer solutions in volatile solvents and emulsions. Previously, dichloromethane and chloroform were used, but ethyl acetate, which has a better toxicological profile, has recently been supplanted. Single-emulsions, such as oil-in-water (o/w), and double-emulsions, such as (water-in-oil)-in-water (w/o)/w, are the two basic approaches used in conventional emulsion manufacturing operations. High-speed homogenization or ultrasonication is required for these operations, followed by solvent evaporation through continuous magnetic stirring at room temperature or low pressure. The solidified nanoparticles were recovered by ultracentrifugation and rinsed using distilled water to eliminate any additional chemicals like surfactants before lyophilization. The particle size is mainly regulated by the polymer concentration, stabilizer, and homogenizer speed [34].

Sono crystallization

Richards and Loomis initially described Sono crystallization (crystallization caused by ultrasonic) in 1927[35]. Due to advancements in ultrasonic equipment, industrial use of Sono crystallization grew in the 1980s, and it is now widely used in the pharmaceutical and fine chemicals industries to generate crystals [36]. To induce crystallization, Sono crystallization employs ultrasound strength in the 20–100 kHz range [34]. Sonication improves micro-mixing, boosts nucleation rate, and lowers particle growth as well as agglomeration. A simple setup and a sizable reduction in the consumption of organic solvents are among the benefits. The downsides are that it is better for making amorphous nanoparticles

and that the immersion depth of the horn tip must be determined experimentally [37]. SAXS (Solution atomization and crystallization by sonication) is a Sono crystallization technique. The anti-solvent receives ultrasonic energy from a bath Sonicator and using compressed air pressure, the solvent is atomized in the anti-solvent [38].

Melt emulsification

The most popular method for producing solid lipid nanoparticles is melt emulsification. Kipp and colleagues firstly prepared ibuprofen nanosuspensions using the melt emulsification process. The technique is divided into four steps. First, the drug is mixed with a stabilizer in an aqueous solution. To make an emulsion, the temperature of the mixture is raised above the drug's melting point and uniformly blended with a homogenizer at great speed.

Bottom-Up NanoCrySP Technology

NanoCrySP is a bottom-up spray drying technology for producing solid particles with drug nanocrystals scattered in a matrix of small molecule excipients. In a nutshell, a drug and excipient solution in a solvent or solvent mixture is spray-dried to produce separate particles in a size range between 2 to 50 m. Each particle is made up of 10 to 1000 nm drug nano crystals. Spray drying is typically performed at temperatures ranging from 40 to 150 °C, whereas spray freezing and freeze-drying are performed in sub-ambient temperatures, distinguishing NanoCrySP technology from traditional solvent removal processes. The NanoCrySP procedure is less expensive than traditional solvent removing techniques, and it also consumes far less time. Patents protect the NanoCrySP technology in India, the United States, and the European Union. NanoCrySP can be used (i) to develop novel chemical entities for pharmaceutical development, (ii) differentiated products of existing molecules, as well as (iii) generic medicinal products [39]. The marketed formulations and current development in nanocrystal formulations shown in table 1 and table 2 respectively.

Application for Nanocrystals

Oral drug delivery

This route for drug delivery is regarded as the most acceptable, safest, and preferable route for administering drugs to the body [40]. For oral absorption of drug molecules, dissolution serves as a rate-limiting phase [41] and Because NCs have a larger surface area for dissolving, they exhibit higher saturation solubility. A higher dissolving rate leads to better medication absorption in the end. As a result, there is a significant drug concentration between the Gastrointestinal Tract as well as the blood vessel, which promotes absorption as well as bioavailability significantly [42]. In the year 2000, Wyeth Pharmaceuticals released the first FDA-approved oral NCs. The formulation contains sirolimus NCs in an excipient mixture that was directly compressed into tablets. When compared to the sirolimus solution, the nanocrystal tablet formulation had 21% better oral bioavailability [43]. As a consequence of the increased bioavailability, the drug dose will be reduced, enabling the drug treatment to be highly inexpensive and minimizing unnecessary drug dumping in the body.

Intravenous drug delivery

The intravenous route has a number of advantages, including 100% bioavailability, rapid onset of action, and a lower dose. But besides these benefits, there are significant drawbacks due to the inclusion of several potentially toxic excipients that might cause serious adverse effects [44]. Nanocrystal technology increases the effectiveness of weakly soluble medicines delivered via the parenteral route. It uses aqueous-based solvents instead of organic solvents, minimizes dosage volume by enhancing drug loading, allowing for quick dissolution (due to nano size), and also prevents macrophage uptake.[45].

Pulmonary drug delivery

The lungs are one of the most perfused organs in the human body that transfer drugs into the systemic circulation efficiently and quickly. Nano-sized particles' adhesiveness on surfaces tends to attach to mucosal surfaces on the absorption site for a longer duration, resulting in a higher absorption rate, as a result, the rate of absorption is increased. The increased residence time at the site of absorption would also help to boost drug uptake by reducing the amount of drug carried outside of the lungs via cilia activity [46]. Drugs are delivered to the lungs in a nebulized form of aqueous nanosuspensions. Nebulizers, either mechanical or ultrasonic, are extensively used for nebulization [47]. Baicalein nanocrystal was prepared for oral and pulmonary delivery. Pulmonary baicalein nanocrystal compared to oral baicalein nanocrystal showed a much faster onset time and a greater baicalein concentration [48].

Ocular drug delivery

Due to the anatomic hurdles and physiologic clearance mechanisms of the blood–neural barriers (BNBs), finding a perfect strategy to administer medications targeting disorders that directly impact the retina and vitreous humor is difficult [49]. Eye drops/solutions, suspensions, and ointments are the most common commercial preparations for ocular drug delivery. The use of these formulations on a regular basis is necessary for the efficient treatment of disorders affecting the anterior region of the eye. Only 1–5% of active components permeate the intraocular tissues due to the anatomical arrangement of ocular tissues, which prevents medications from penetrating through the cornea [5].The dispersibility difficulties of poorly soluble pharmaceuticals are addressed by nanocrystal technology. The preparation of hydrocortisone nanocrystals improved bioavailability (two times) and sustained drug delivery (1.8 times) when compared to the drug solution [50]. Polycarbophil and poloxamer were used as gel components in the in-

situ gel formulation of forskolin nanocrystals, with a pharmacological action lasting up to 12 hours [51].

Topical Drug Delivery

The main physiological barrier to topical medication administration is the stratum corneum [52]. The capacity of a dermatological medicine to pass through the skin in adequate amounts to have the required therapeutic effect is critical to its efficacy as systemic drug delivery[53].NCs are thought to be capable of forming an occlusive barrier by clumping together tightly enough to wet the skin and thus increase medication permeability. Furthermore, dispersed NCs stayed on the skin during the time, allowing the medication to be released in a sustained manner [54]. Lutein nano crystals were formulated, and permeability across cellulose nitrate membranes, used as an in vitro model, was 14 times higher for lutein nano crystals than for lutein coarse powder [55].

Targeted Drug Delivery

Nanosuspensions help to target certain organs depending on surface modification properties. By adjusting the stabilizer, the in vivo behaviour can be readily changed. The mononuclear phagocytic system would pick up the drug, allowing for focused drug distribution. When macrophages are not the targeted targets, the natural targeting mechanism may present challenges. As a result, its surface potential must be changed in order to avoid phagocytic uptake of medicines [56]. Kayser created an aphidicolin nanosuspension that he claimed was highly active at microgram concentrations and improved therapeutic targeting to leishmania-infected macrophages [57]. Scholer et al. discovered that an Atovaquone nanosuspension increased drug selectivity to the brain in the cure of Toxoplasmic Encephalitis [58].

Table 1: Marketed formulation of nano crystals

Trade name with API	Uses	Applied technology	Manufacturer	Formulation
Rapamune (Rapamycin)	Immunosuppressive drug	Wet Bead Milling	Wyeth	Tablet
Emend (Aprepitant)	Used as anti-emetic	Wet Bead Milling	Merck	Capsule
Tricor (Fenofibrate)	Hyperlipidemia	Wet Bead Milling	Abbott	Tablet
Megace ES (Megestrol)	Used as Anti-anorexic	Wet Bead Milling	Par P'ceutical Companies	Suspension
Triglide (Fenofibrate)	Hyperlipidemia	Wet Bead Milling, High pressure homogenization	Skye Pharma Inc.	Tablet
Nucryst® (Silver)	Prevent bacterial infection	Reactive magnetron sputtering	Nucryst Pharmaceuticals	Acticoat
Gris-Peg® (Griseofulvin)	Prevent fungal infection	Precipitation Method	Novartis	Tablet
Avinza® (Morphine sulphate)	Anti-chronic pain	Wet Bead Milling	King Pharma	Capsule
Verelan PM (Verapamil HC)	Used as Anti-arrhythmia	Wet Bead Milling	Schwarz Pharma	Capsule
Azopt® (Brinzolamide)	Treat Glaucoma	Wet Bead Milling	Alcon	Suspension
Ritalin LA® (Methyl-phenidate hydrochloride)	Used as Anti-psychotic	Wet Bead Milling	Novartis	Capsule
FocalinXR® (Dexmethyl- phenidate hydrochloride)	Used as Anti-psychotic	Wet Bead Milling	Novartis	Capsule
Herbesser® (Diltiazem hydrochloride)	Used as Anti-angina	Wet Bead Milling	Mitsubishi Tanabe Pharma	Tablet
Zanaflex™ (Tizanidine hydrochloride)	Used as Muscle relaxant	Wet Bead Milling	Acorda	Capsule
Naprelan® (naproxen sodium)	Anti-inflammatory	Wet Bead Milling	Wyeth	Tablet
Theodur® (Theophylline)	Treat Bronchial dilation	Wet Bead Milling	Mitsubishi Tanabe Pharma	Tablet, Capsule
Cesamet® (Nabilone)	Used as anti-emetic	Precipitation	Lilly	Capsule
Invega Sustenna® (Paliperidone palmitate)	Treat major depressive disorder	Wet Bead Milling, High pressure homogenization	Johnson & Johnson	Tablet

Table 2: Current study and development of Nano crystal formulations.

Study	Drug	Stabilizers	Purpose	References
Formulation and optimization	Itraconazole	Pluronic® F127, HPMC K100	Thermosensitive in situ ocular gel	[61]
Development and evaluation	Aceclofenac	Tween 80, Poloxamer 407, and PEG 6000	Enhancing solubility	[62]
Formulation and in vitro and in vivo evaluation	Budesonide	Pluronic F-68	Nanocrystal-embedded microparticles dry Powder for inhalation	[63]
Formulation development, in vitro and in vivo evaluation	Lutein	Soy phosphatidylcholine	Enhance aqueous solubility and oral bioavailability	[6]
Formulation and optimization	Meloxicam	PEG 4000, PVP K25, Poloxamer 188	Oral lyophilisates	[64]
Formulation, characterization	Risperidone	Pluronic® F-68, Pluronic® F-127, PCL, PVA and SDC	Enhance water solubility	[65]
Formulation and evaluation	Rutin	PVA 1788, PVP K30, HPMC, SDS, Poloxamer 188, and Tween-80	Nanocrystal anti-photoaging gel	[66]
Formulation and evaluation	Camptothecin	Boric acid	Enhance Anticancer activity,	[67]
Formulation and evaluation	Camptothecin	Hyaluronic acid	Enhance Anticancer activity	[68]
Formulation and Evaluation	Amisulpride	HPMC, PVA, β-cyclodextrin, Sodium Laurel Sulphate	Nanocrystal Tablet	[69]
Design, Development, and In Vitro Evaluation	Flurbiprofen	poloxamer 188 and hydroxypropyl methylcellulose E15	An oral thin film by nanosuspension technology	[70]

Characterization of Nano crystals

Mean particle size & Particle Size Distribution

Dynamic light scattering (DLS), often referred to as photon correlation spectroscopy (PCS), is typically used to make the measurement. It uses laser irradiation of particles to monitor Brownian motion, and by examining the variations in scattered light's light intensity, it connects Brownian motion to particle size. Particle size and the PI all impact the saturation solubility, dissolving velocity, and biological efficiency. When PI ranges from 0.1 to 0.25 it denotes a narrow size distribution, while PI larger than 0.5 it denotes a relatively wide distribution. Laser Diffractometry (LD) is used to analyse PCS nanosuspensions. The LD measures particle sizes varying from 0.05 to 80 meters up to 2000 meters. Particle shape is visualized via atomic force microscopy [71-73].Small-angle X-ray scattering (SAXS) uses the X-ray small-angle scattering effect to measure the particle size distribution of nanocrystals. This is a straightforward, highly accurate procedure, but it is also fairly pricey. It typically has a measurement range of 1-300 nm for particle size dispersion.

Surface Morphology

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are frequently applied to characterize the morphological appearance of drug nanocrystals. SEM scans the sample with narrowly focused, highly energetic electron beams. The resolution can reach 1 nm, and the stereo image effect is good. TEM projects accelerated and aggregated electron beams onto the extremely thin sample using an electron beam as the light source. The sample's thickness must be less than 100 nm for the electron beam to pass through. The current resolution is up to 0.2 nm [34].

Zeta Potential (Particle charge)

The zeta potential (particle charge) regulates the physical reliability of the nano crystals, which is influenced by the stabilizing agent and the pharmaceutical ingredient itself. Minimal zeta potential of ± 30mv is necessary for electrostatically stable nano crystals. A minimum of 20mv is needed in combination stearic as well as electrostatically stabilized nano crystals.

Crystal/ Structural Morphology

Differential scanning calorimetry (DSC), a method to obtain heat flow (dq/dt) in and out of a specimen cell in a controlled environment and over a large temperature range [34]. It also is utilized to figure out what kind of crystal structure it has. Since drug particles are transformed to an amorphous form during the preparation of nanosuspensions, it's indeed necessary to quantify the amount of amorphous drug produced. X-Ray Diffraction (XRD) is utilized to determine amorphous drug changes in physical condition and extent [24].

Saturation solubility and dissolution velocity

The nano crystals boost both saturation solubility and dissolving velocity. Saturation solubility is a compound-specific amount that varies according to temperature and dissolving medium conditions. the Kelvin equation as well as the Ostwald-Freundlich equations explains increases in saturation solubility[24].

Stability Study

The stability of nano crystals includes chemical stability (degradation and spoilage) and physical stability (sedimentation, agglomeration, crystal growth, and crystalline state) [74,75]. The particle size alteration in the storage at 2-8°C was employed to check the stability of the improved nano crystal formulation. A particle size analyzer can be used to monitor any changes in particle size in the nanocrystal formulation at regular intervals [34].

CONCLUSION

Nanocrystals have been shown to be a viable technique for addressing pharmaceutical drug solubility issues. The nanometer size of NCs allows for a significant increase in solubility as well as dissolution, making it easier to improve the efficacy of poorly soluble drugs administered via intravenous, oral, ocular, pulmonary, and transdermal routes. Initially, sustained release, customized drug delivery, and drug targeting were the primary goals of nano crystals, but their application has evolved to include new goals in recent years. As a result, nano crystals are now being used to achieve pharmacological goals that polymeric nanoparticles have been used for decades to attain. They, like polymeric nanoparticles, exhibit negative stability tendencies, such as aggregation or a change in the solid state of the medication, which must be carefully addressed in the preparation of efficient formulations. It is capable to produce a delayed or targeted release by changing the surface of the nano crystals

ACKNOWLEDGEMENTS

The authors would like to thank principal of the institute for their kind support and continuous encouragement.

Conflict of interest: The authors have no conflicts of interest.

Funding support

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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