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Review Article

The Evolution of Nanocrystalline Drug Delivery System

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Abstract

Developing nanocrystalline drug delivery technologies is a noteworthy advancement in pharmaceutical science. The nanocrystalline formulations aim to improve therapeutic efficacy, pharmaceutical solubility, and bioavailability. We develop many methods for their fabrication, with top-down, bottom-up, and combination procedures, beginning with reasoning behind nanocrystalline approaches. In this type of review, we focused on the progress of nanocrystalline drug delivery systems in various years by applying different techniques which started in 1990 and what dosage forms are still made by this technology. It is found that various other techniques are also there manufacturing of drug Nanocrystals through years of investigation made by specialists. The researchers found methods such as Top-down, bottom-up, combination, solvent displacement technology, fluidised bed technology, freeze drying, spray drying, electrodynamic technique, and melt emulsification. Every process has advantages and disadvantages, therefore selecting the proper technology is critical to produce drug nanocrystals successfully.

Keywords: Nanocrysyals, CT, Bottom-up, Top-Down, HPH, Nanocarriers

1. Introduction:

There is a major hurdle in pharmaceutical industries related to drug solubility and its dissolution so, to overcome that problem nanotechnology arises by that Drug particle size is reduced by various techniques and drugs particle size is reduced after the solubility of that particular drug increases in various solvents. Early years (1960s–1990s) Although the idea of employing nanoparticles to deliver drugs first surfaced in the 1960s, nanocrystals as a drug delivery system weren't created until the 1990s. Earlier studies concentrated on employing nanocrystals to increase the bioavailability of medications with low solubility. Then in 1990, one novel technology was invented known as Nanocrystal technology [1]Nanocrystal technology is also part of nanotechnology which makes Drug nanocrystals with the help of one or more stabilizers and in that chemical transformation also occurs Nanocrystal technology has various methods- Top-Down, bottom-up, Combination, H69, H42, Antisolvent Precipitation, and CT method, also known as the Nanoedge technique[1].

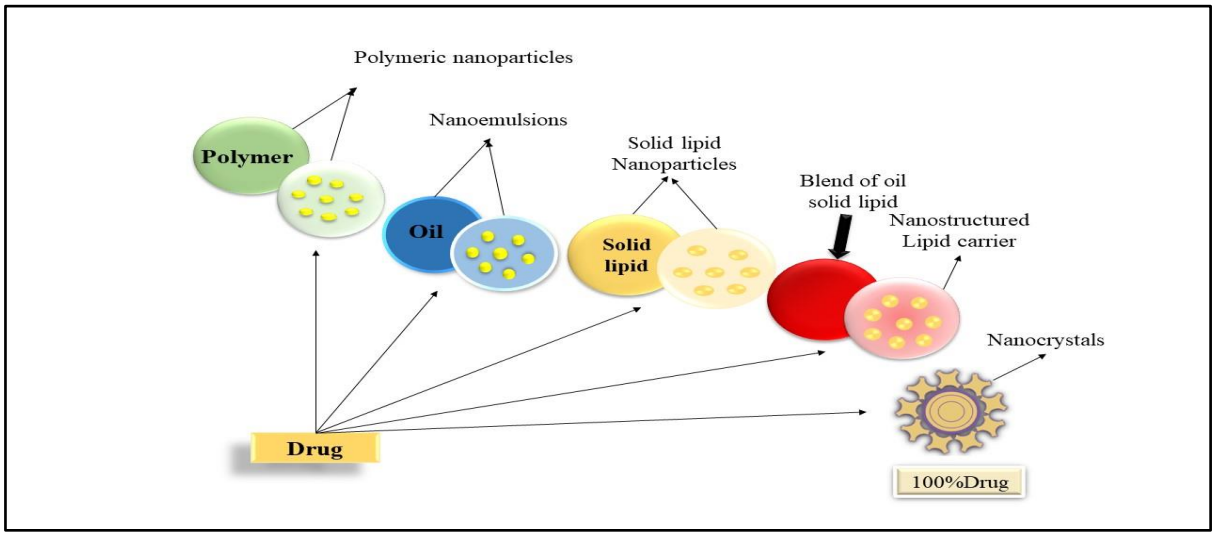

Figure 1: Percentage of drugs concerning different formulations[8]

The transition between electrical energy level spacing and temperature occurs at a relatively large size for a given temperature in semiconductors, as opposed to hard metals, insulators, and molecular nanocrystals. Initially, any material with significant Differences in the fundamental characteristics of electrical and optical systems will be observed. As cluster size increases, the band's centre develops first, followed by its edges[1]

Nanotubes of carbon and fullerenes in nanocrystals are only a few nanomaterials widely produced and used thanks to nanotechnology. Although not much research has looked at the cellular toxicity of "artificial nanomaterials," many are considered safe for the environment and humans. Because artificial nanoparticles are easily absorbed and stored in the body and environment, they can interfere with the functions of living things that depend on intricate natural nanomaterials[1].

Nanocrystals are very small particles with dimensions at the nanoscale generally in 10 to 500nm and another termed Smartcrystals range in 10 to 100nm. Crystal solid API particles 100% with measurement in the nanometer assortment that are carrier-free due to their high drug loading capacity nanocrystal have become more attractive for choice of formulation for different diseases[1], associated with other nanoparticles like polymeric nanoparticles, the high drug loading of NCs ensures effective medicament delivery to cells or tissues and maintains potent therapeutic concentration to induce desired therapeutic activities. In addition increasing a drug's solubility, Liquid dispersions of raw drugs stabilized with a polymer or surfactant are called nanocrystals. A drug formulation as nanocrystals enhances skin penetration and absorption because of enhanced solubility and extended retention at the specific site's also, changes its pharmacokinetics, biodistribution, and therapeutic effectiveness[6]. These particles show unique properties or characteristics because of low particle magnitude and construction, making them promising various applications in medicine, energy, and electronics[7]. Low topical bioavailability and limited skin penetration are two problems with conventional topical administration systems. Liposomes, solid lipid nanoparticles, liposomes, transferases, ethosomes, nanostructured lipid carriers, nanoemulsions, dendrimers, and micelles are just a few of the nanotechnology techniques that have overcome these limitations[8]. but nanocrystals are more stable than other nanocarriers which are stabilised by appropriate surfactant or polymeric stabilisers[9]. There are several different kinds of stabilisers, including synthetic or biodegradable surfactants and stabilisers, as well as electrostatic or electrostatic stabilizers such as poloxamers-polyethylene glycols (PEG), Polyvinyl alcohol (PVA), ionic surfactant (e.g. sodium dodecyl sulfate-sds), SLS, chitosan and non-ionic surfactants (tweens and black copolymer of (ethylene oxide)-poly (propylene oxide)[2], proteins (ß-lactoglobulin, ß-casein, bovine serum albumin. Ionic surfactants stabilise NCs by electrostatic repulsions, while polymers and proteins cover them via steric repulsions[3]

2. Evolution of nanocrystals:

Nanocrystal technology has been created and explored for decades, dating back to the late twentieth century. The discovery and understanding of nanocrystals progressed alongside advances in nanoscience and nanotechnology. Early research focused on grasping the basic characteristics and manufacturing processes of nanocrystals. The variety of materials that might be utilised for nanocrystal synthesis was increased by developing new processes like precipitation-ultrasonication, precipitation-antisolvent, high-pressure homogenisation, Emulsification, Lyophilization, and media milling were employed. Here are some key highlights of the evolution of nanocrystals:

Table 1: Nanocrystals evolve during their formative years.

Year	Development
1998-1990	The groundwork for nanocrystal technology was laid in the 1980s and 1990s when nanoscience emerged as a distinct field of research. Scientists began researching the formation and properties of nanoscale materials such as semiconductor nanocrystals and quantum dots[38].
1990	The American physicist and chemist Louis E. Brus first used the term "quantum dots" in 1990. Semiconductor nanocrystals with special electrical characteristics are known as quantum dots. Their size-dependent optical and electrical properties made them the centre of attention for nanocrystal research[39].
1993	Paul Alivisatos, a pioneering scientist in the field, established the creation of colloidal nanocrystals using wet chemical procedures. This work represented a significant step towards the advancement of solution-phase synthesis methods.
1990-2000	By applying various techniques researchers make a major impact on the progress of controlling the size, shape and composition of nanocrystals. progressive characterization techniques are utilized high-resolution microscopy and spectroscopy are employed to study nanocrystal properties[40].
2000	In the late 1990s and early 2000s applications Emerged, and researchers began investigating nanocrystal applications in industries such as electronics, photonics, catalysis, and biomedical imaging[41].
2000	In 2000, Rapamune (sirolimus), the first FDA-approved drug product containing nanocrystals, was announced. This was a major turning point for the field of nanomedicine and opened the door for more advancements in the creation of drug delivery systems using nanocrystals[42].
2000-2010	Nanocrystal-based technologies began to emerge from the research lab and into commercial applications. Quantum dots, in particular, have found use in screens, solar cells, and imaging for medical purposes[43].
2010-ahead	Nanocrystal technology continued to evolve as synthesis techniques, materials engineering, and application development progressed. Research has expanded to cover energy storage, medicinal delivery, and quantum computer science[44].

2.1 Recent Development: Nanocrystals' use to deliver vaccines, other biologics, and gene therapy agents has gained popularity in recent years. New methods for regulating the release of medications from nanocrystals are being developed by researchers, which may enhance the effectiveness and security of these drug delivery systems[10].

Table 2: Evolution of Nanoformulations [11]

Sr. No	Formulation	Year
1	Spansule	1952
2	Liposome	1964
3	Ocusert	1974
4	OROS	1975
5	Delsym	1982
6	Lupron Depot	1989
7	Norplant	1990
8	Doxil	1995
9	Rapamune	2000
10	Onpattro	2018
11	Rebelsus	2019

Advancement of Nanocrystal Production Technology: There are new methods have been developed over time, including electrohydrodynamic methods and supercritical fluid technology. These methods allow for the creation of nanocrystals with controlled surface properties, size, and shape. A promising method for producing nanocrystals on a large scale is continuous-flow microfluidic.

Fabrication of Nanocrystals: Various techniques have been used to generate NCs. The NCs have a small amount of stabilizer-coated NCs due to the steric or ionic stabilisation effect, and they have 100% drug loading. Describes the various stabilisers, production techniques, and administrative routes for NCs. There are three basic types of NC preparation techniques: bottom-up approaches (crystal growth or nucleation), top-down approaches (Canonization), and combination techniques.

2.2 Top-down Method: In the top-down method, drug crystals that have been micronized are subjected to high-pressure collisions or mechanical attrition, which reduces the particle size to the nanometer range. High-pressure homogenization (HPH) and milling are the main methods utilised to achieve this. Top-down techniques, commonly referred to as "Canonization," involve bringing coarse drug particles down to a nanometric (nm) range in size[12]

2.2.1*Media Milling:* Milling time can range from hours to days, depending on the drug's characteristics, milling media, and degree of particle size reduction. Crystal imperfections may occur as a result of milling-induced surface disordering. Furthermore, as particle size decreases, a hydrophobic surface may be visible. The subsequent products may become physically and chemically unstable during storage as a result of crystal defect rearrangement and amorphous region re-crystallization.it is found that by milling surface area is increased and solubility is increased[12].

2.3 Bottom-up method: The bottom-up drug nanocrystal production approaches rely on the controlled precipitation of drug molecules into nanocrystals. The most thoroughly investigated production approaches include solvent-antisolvent precipitation (conventional in bulk and using microfluidics), supercritical fluid precipitation, solvent evaporation (spray dryer), and temperature decrease (frozen dryer).

2.3.1 *Antisolvent precipitation method:*

The process of vigorously mixing a drug solution in an organic solvent that is miscible with water into an antisolvent—typically water or another aqueous media—creates supersaturation conditions in the aqueous phase, causing drug molecules to nucleate and precipitate, resulting in the formation of nanosized drug nanocrystals. This is the fundamental concept underlying the solvent-antisolvent precipitation approach for manufacturing medication nanocrystals. The nucleation process is triggered by a change in the system's free energy (ΔG crystal), which is proportional to the crystal size. To allow the nucleation process to occur, an energy barrier must be broken through. Temperature and supersaturation conditions influence the critical size at which crystal nuclei form.

Table 3: shows the evolution of nanocrystals and nano co-crystals formed using standard antisolvent precipitation[45].

Technique	Drug	Outcome	Year
Solvent-antisolvent precipitation	Itraconazole Beclomethasone Propionate Celecoxib	Nanocrystals, <300 Nanocrystals, <100 Nanocrystals, 291– 442 nm	2006 2010 2014
Sonoprecipitation	Aceclofenac Nifedipine Avanafil Caffein:Maleic Acid 2:1	Nanocrystals, 112 nm, PDI 0.1655 Nanocrystals, 209 nm Comparison between top-down and bottom-up approaches, 128–4868 nm Formation of co-crystals from substances non-congruently soluble	2017 2010 2017 2010
High Gravity Controlled Precipitation	Cephradine	Nanocrystals, 200–400 nm	2005
High Gravity Antisolvent Precipitation	Cefuroxime axetil Danazol	Amorphous nanoparticles, 300 nm Nanocrystals, 190 nm	2006 2009
Evaporative	Itraconazole	Higher dissolution	2005

2.3.2 *Supercritical Fluid Technology*:

Supercritical fluid (SCF) technology has been utilised to change the solid-state characteristics of powdered active ingredients, particularly those that are poorly soluble in water. Size, crystallinity, polymorphism, shape, and surface are some of the properties that change after supercritical precipitation.

Table 4: Evolution of supercritical fluid technology[46]

Technique	Role of the SCF	Compound	Size	Outcome	Year
RESS	Solvent	Digitoxin	70–460 nm	EtOH used as a co-solvent	2010
		Carbamazepine	430–900 nm	Production of pure crystals of monoclinic polymorph	2012
		Aspirin	100–300 nm	Decreased crystallinity by XRD, spherical crystals	2005
		Loperamide	300-500 nm	No evaluation of the crystalline status	2006
		Raloxifene	19–137 nm	Nanocrystals, reduction in the crystallinity in XRD	2012
		Ibuprofen	7–250 nm	Nanocrystals by XRD	2016
		Olanzapine	191 nm	Nanocrystals by DSC	2016
SAS	Antisolvent	Camptothecin	250 nm	Nanocrystals with a lower degree of crystallinity by XRD	2010
		Lysozyme	70–100 nm	The biological activity of the protein retained	2008
		Amoxicillin	200–900 nm depending on the parameters chosen in the process	Nanocrystals	2010
		Apigenin	400-800 nm	Spherical structure, no changes in the crystalline structure	2013

2.3.3 Solvent *removal technique:* The elimination of solvents is the foundation of these approaches. Traditional techniques, such as spray drying and freeze-drying, cannot produce nanoparticles because more efficient liquid atomization is required. Both ways of producing nanoparticles use increased atomization.

During spray drying, a medicine solution, whether organic or aqueous, is atomized into tiny droplets, which evaporate in a heated air current to form dry particles. In the 1980s, spray drying was examined as a possible alternative for producing fine particles. When the pulmonary route was proven to be a viable method of delivering therapeutic proteins, much effort was put into spray-drying pharmaceuticals in the early 1990s.

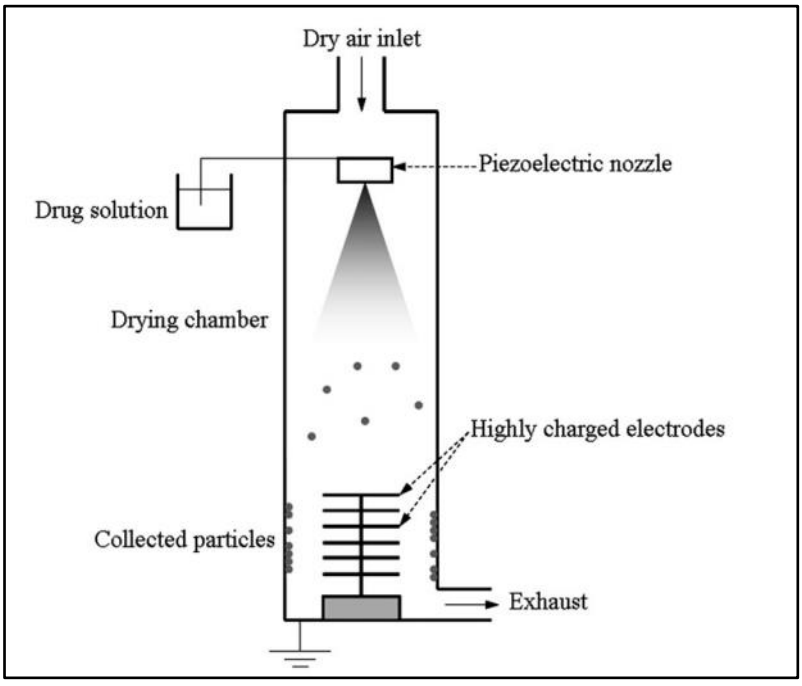

Figure 2: Spary dryer[47]

2.4 Combination Method: The combination method is now an emerging technique for nanocrystal formulation with particle size reduction with smaller nanometres that are less than 100nm. Overcome the problem associated with the Top-down and bottom-up technology. In nanocrystal technology, the concept of "combination method" describes the use of multiple methods or strategies in the synthesis, functionalization, and use of nanocrystals. With this approach, researchers can leverage the power of several approaches to extract more features or specialised functions. In combinative technique, there are H69, H42, and CT methods which are generally known as Nanoedge technology[13]. In this Technology firstly drug suspension is formed by giving a stirring effect and after that suspension is passed through a high-pressure homogenizer in that process HPH piston applies pressure on the Drug-stabilizer suspension and it will reduce its particle size, but because of Ostwald ripening and sedimentation occurs therefore to avoid that problem we could use a Freeze drying and spray drying for that 5% Cryoprotectant ought to be added in the nanosuspension to preserve drugs pharmacological action solidification of nanocrystals by solid formation nanocrystal stability will increase and that nanocrystals having the splendid effect of desire pharmaceutical action[14]. Drug nanocarriers (NCs) avoid potential adverse effects and stability difficulties associated with standard encapsulation designs. In the combination method, Careful nucleation management occurs through a thorough grasp of the relevant solution's metastable zone required for carrier-free NC formation. Without forming, a solution might remain supersaturated and become metastable absorbing any nuclei. The metastable zone width denotes the maximum level of supersaturation that occurs. Direct nucleation from the metastable zone promotes the development of homogeneous nuclei, hence facilitating the formation of uniform NCs[15]. Combinatorial approaches to particle size reduction improve the efficiency of conventional procedures while addressing their shortcomings. There are five recognised combinative methods: H 69 (microprecipitation immediately followed by HPH, also called "cave-precipitation"), H 42 (spray-drying followed by HPH), H 96 (freeze-drying followed by HPH), and CT (media milling followed by HPH). NANOEDGE is the method that uses microprecipitation followed by HPH.

2.4.1 *Nanoedge Technology*: The first combinative particle size reduction technique developed for the production of medication nanosuspensions was Baxter's NANOEDGE technology. This manufacturing process includes a solvent-antisolvent step known as microprecipitation, followed by a high-energy procedure. First, the medication is dissolved in a suitable solvent, usually an organic solvent that is water soluble. The drug solution is then combined with a second aqueous liquid that contains less soluble drug. An infuser device, for example, is used to carefully add the aqueous liquid to the drug solution. It may contain surfactants to help it stay stable. The precipitation occurs as a result of the solubility change. Microprecipitation is a pretreatment method that produces either amorphous or semicrystalline drug particles. The drug particles are then shrunk and transformed into a more stable crystalline state via a high-energy annealing step, similar to high-pressure homogenization[2]. The annealing step enhances nanosuspensions' thermodynamic stability by preventing precipitated particles from growing to micrometre size.

Nanoedge applications:

This technology could create drug nanosuspensions with higher drug loads and more flexible administration options, such as injectable and oral routes.

In comparison to the control formulation, the nanosuspension formulation utilising the NANOEDGE process enhanced bioavailability in rat models by as much as 30 times.

2.4.2 *H69 Technology:* Mueller and Moschwitzer developed the H 69 process, which is part of the Smartcrystals technology family. The NANOEDGE method is similar to this combinatorial process. It uses high-pressure homogenization to reduce particle size, followed by an organic solvent-based microprecipitation step. The H 69 technology differs in that the cavitation occurs either simultaneously with the formation of the particles (known as "cave-precipitation") or at most two seconds after. Different pump rates can be adjusted to achieve this. The drug precipitates as a result of the interaction of the liquid fluxes. Particle formation happens in a homogenizer's high-energy zone, where cavitation, particle collision, and shear forces are immediately applied to the freshly formed drug particles[16].

H69 Applications:

After five minutes, the results increased to 27 nm, and six minutes later to 22 nm. The medicine nanocrystals disintegrated as a result of the increased dissolving pressure at these small particle sizes.

2.4.3 *H42 Technology*: Moschwitzer developed the H42 method, which is part of the Smartcrystals technology platform. In this combinatorial technique, spray drying (SD) is employed as a precipitation and pretreatment phase, whereas HPH is used to minimise particle size. During the bottom-up process, the organic solvent is removed, distinguishing this technique from the NANOEDGE and H69 techniques. The weakly soluble chemical is dissolved in organic solvents during the first unit operation (SD). The choice of solvent is critical to increasing process efficiency. To ensure an efficient process and solvent-free spray-dried powders, the ideal organic solvent should have strong dissolving properties, as well as an adequate boiling temperature and vapour pressure. Furthermore, the solvent of choice should be as non-toxic as possible[17]. The H 42 combinative approach has several advantages, including tiny drug nanocrystals that require fewer HPH cycles, solvent-free dry intermediates, and relatively short processing times during SD. One of its disadvantages is that it uses high temperatures during SD, which may make it unsuitable for processing thermolabile compounds.

H42 Applications:

Differential scanning calorimetry (DSC) was utilised to determine that the crystallinity of spray-dried ibuprofen powders remained essentially unchanged when compared to the raw material.

The melting points and normalised melting enthalpies of the original and spray-dried modified ibuprofen were remarkably similar. In this case, the greater friability of the starting material was associated with improved reduction efficacy rather than a change in the drug's solid-state behaviour**.**

Improve drug structure which shows spherical drug particles, portions of the surfactant improved the flowability and mill-ability of spray-dried powders. However, high surfactant concentrations (i.e., a drug/surfactant ratio of 1:1) hurt the powder characteristics as well as the efficacy of the subsequent particle size reduction.

2.4.4 *H96 Technology*: Oschwitzer and Lemke developed the H 96 combinative technology, which is part of the Smartcrystals technology family (Abbott/Soliqs, Germany). The procedure begins with freeze-drying (FD), followed by high-pressure hydrolysis (HPH), which reduces the size of the particles. Organic solvents, like those used in the H 42 process, are eliminated at the bottom-up stage. Organic solvents are employed in the FD stage to dissolve poorly soluble medicines. Following that, the medicinal solution is freeze-dried and frozen again with liquid nitrogen (instant freezing or snap-

freezing). Drug pretreatment alters the starting material in an attempt to improve HPH's efficacy in particle reduction[18].

To enhance the quality of the freeze-dried powders as well as the technique itself, the solvents must be carefully chosen. The freezing point, vapour pressure, and toxicity of the solvent are all important factors that influence process performance. It is critical to use organic solvents with relatively high freezing points for FD applications. This ensures that the solvent crystallises completely throughout the lyophilization process. The chosen solvent should have a high vapour pressure to ensure complete elimination during the first drying cycle. To ensure patient safety and product quality, organic solvent residues must be eliminated[19,20].

The H 96 technology's low temperatures and high FD yields make it ideal for processing costly or thermally stable medicines. Furthermore, the lyophilization procedure removes the organic solvent component, resulting in nanosuspensions that are suitable for use or processing. One of the disadvantages of lyophilisation is that it takes longer.

H 96 Applications:

Synthesis Techniques:

Hybrid Method: Researchers regularly use both bottom-up and top-down manufacturing strategies. For example, start with a larger material and refine it further through controlled growth (bottom-up) after breaking it down into nanocrystals using wet-chemical processes.

Multistep Synthesis: To create nanocrystals with a certain size, shape, and composition, different techniques may be used in progressive or multistep synthesis procedures.

Surface functionalisation:

Sequential Coating: Nanocrystals' stability, biocompatibility, and reactivity can be increased by mixing multiple coating materials or changing the surface through sequential deposition methods.

Hybrid Ligands: Researchers can tailor the surface chemistry of nanocrystals to particular applications by mixing several ligands or surface modifiers.

Quantum dot technologies:

Multicolour Quantum Dots: Multicolour imaging probes in biology and optoelectronic devices can be developed by combining multiple types of quantum dots with different emission wavelengths.

Hybrid Quantum Dot Structures: By merging quantum dots with other nanomaterials such as graphene or carbon nanotubes, hybrid structures with superior electrical or optical properties can be formed[21]. due to their distinct chemical, optical, and electrical properties that set them apart from other materials[22].

Environmental and green synthesis:

Eco-friendly Approaches: The combination of conventional and green synthesis techniques enables the development of environmentally friendly nanocrystal synthesis technologies[23].

3. High-pressure homogenizer:

This is an instrument which is used for the fabrication of nanocrystals by a high-piston pump. Principles of piston-gap homogenization or microfluidization are applied in the HPH method. A chamber of the Y-or Z-type makes up the microfluidizer apparatus. Divided into two streams that collide frontally by the Y-type chamber, the coarse drug suspension is separated. In 1996, Ljusberg-Wahren published the first description of this approach. By using dispersions from a liquid-crystalline phase, the top-down approach is the most popular technique for creating LCNPs. An amphiphilic material (phase-forming lipid) is first hydrated with the aqueous phase and stabilisers in this technique, which has been documented since the 1990s. The TD technique requires a significant amount of energy, which can be supplied by high-pressure homogenization, sonication, or shearing. This energy eventually causes fragmentation, resulting in controlled-sized nanoparticles with low polydispersity[24]. For the preparation of nanoparticles using HPH, a premix could be a coarse emulsion, dispersion or suspension[25].

Techniques are extremely energy-intensive and efficient[26] for example, using high pressure up to 1500 bar during the homogenization process, 50 to 100 cycles are still required to achieve the desired particle size and size distribution. Numerous parameters, such as particle size distribution, reduction, zeta potential, stability, drug release profile, microscopic evaluation, bioavailability studies, process optimisation, cost-effectiveness, and so on, are commonly used to evaluate the use of a high-pressure homogeniser in nanocrystalline drug delivery systems. The formulation of a nanocrystalline drug delivery system can be altered using a high-pressure homogenizer based on the drug, excipients, and intended application.

Table 5: HPH development for the nanoformulations

Year	Development
1990	Gary Liversidge and his colleagues from Sterling Drug Inc./Eastman Kodak have applied a wet media-based milling technique (wet ball milling, WBM), adapted from the paint and photographic industry, to reduce the particle size of poorly water-soluble drugs[27].
1994	Müller and his colleagues have developed an alternative technology based on piston gap high-pressure homogenization (HPH) to produce nanosuspensions[27].
1999	Technology has developed another variant of a piston-gap homogenization process, which is conducted with water-reduced or even water-free liquids as dispersion media[27].

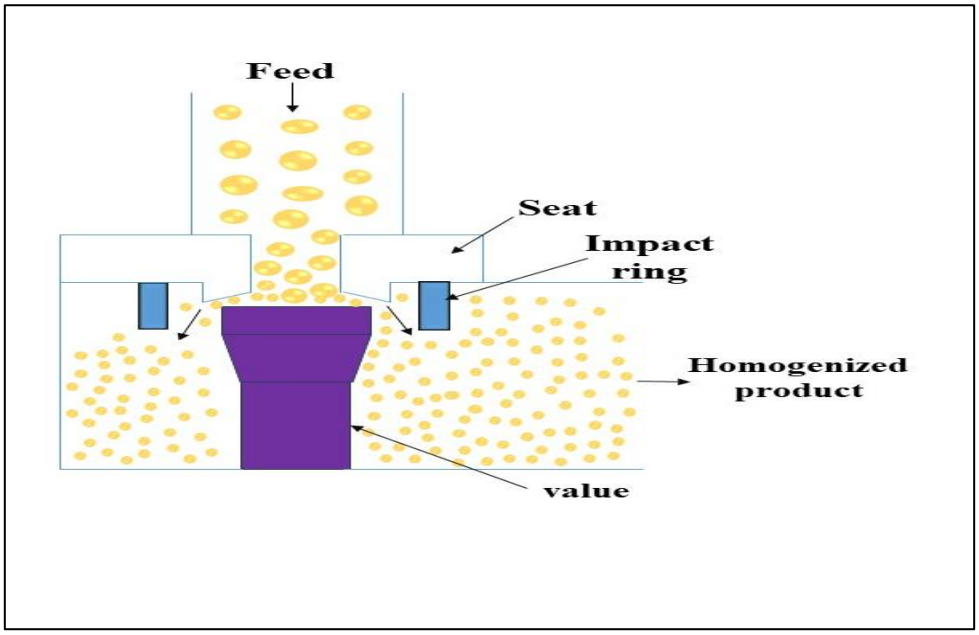

Figure 3: High-pressure homogenizer[48]

Advantages:

- Simple to use
- Fast as compared to other
- Avoid organic solvents
- High reproducibility
- Easy scale up

Disadvantages:

- Energy-intensive technique.
- The possible instability of medications due to higher shear and temperature**.**
- The grinding media could cause product contamination.

4. Applications of Nanocrystals

4.1 Oral delivery

Oral delivery of NCs is primarily examined via oral, ophthalmic, pulmonary, parenteral, and cutaneous routes, all demonstrating their significant therapeutic usefulness[28]. Because of the numerous benefits, the oral route is the most popular and is regarded as the safest and most appropriate method of medication delivery. NCs provide answers to solubility-related issues such as low/variable bioavailability, delayed start of action, variation in bioavailability due to fed/fast conditions, and high oral dose utilisation. Absorption in both fasted and fed states can be a permeability-limited process, eliminating the absorption differential caused by dissolution differences.

4.2 Parenteral delivery

Administering poorly soluble compounds intravenously (i.v.) with cosolvents, surfactants, liposomes, or cyclodextrins can result in toxic side effects or large injection volumes. Because NCs have a small particle size and a safe composition, NPS can be injected intravenously (IV) for 100% bioavailability, quick action, and lower dosage. For example, many nanocrystal lyophilized products are administered parenterally for that nanocrystal formulation size should be less than 100nm[16,29]. Long-circulating nanocarriers, also known as "stealth" systems, have been developed to provide nanosystems with long circulation properties while preventing NCs or nanocarriers from being quickly removed from circulation[30]. Hydrophilic polymers can be used to coat surfaces, resulting in stealth particles that prevent opsonization[31].

4.3 Ocular, pulmonary and dermal delivery

Drug delivery into the ocular cavity is difficult due to the eye's physiological barriers and the critical pharmacokinetic environment[32]. Topical instillation is the most common non-invasive method of administering medication to treat conditions affecting the eye's anterior segment[33]. In terms of increased ocular bioavailability, the significance of both nanosized particles and topical nanocrystal suspension properties, such as the absence of irritation due to their small size, appropriate viscosity, and mucoadhesiveness, has been extensively documented[34].

4.4 Control delivery system

Nanocrystals, which are typically between one and one hundred nanometres in size, can be used to deliver therapeutic agents, such as medications or imaging agents, to specific body targets in a controlled manner. Nanocrystals are advantageous for controlled delivery applications due to their small size, high surface area-to-volume ratio, tunable surface properties, and ability to encapsulate and release drugs in a controlled manner. Overall, the use of nanocrystals in controlled delivery applications has tremendous potential to improve the efficacy and safety of therapeutic interventions in a variety of disease areas, including cancer, infectious diseases, and inflammatory disorders[35].

Conclusion:

This leads to the conclusion that nanocrystal evolution has a substantial impact on nanotechnology, and as a result, researchers and practitioners benefit from the development of nanocrystal technologies. Nanocrystals are more significant than other nanocarriers because they hold a higher concentration of medication and are more stable. CT, H69, H96, and H42 are examples of new technologies discovered during evolution. This study focused on evolution and its usefulness in helping researchers learn about nanocrystals.

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