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Nanocrystal in Drug Development: Regulatory Perspective and Emerging Pharmaceutical Innovation

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ABSTRACT:
The pure drug crystals, sometimes referred to as nanocrystals, are used in drug research to improve the delivery of drugs that are not very soluble in water: Nanocrystals, or nanosized particles, are made by combining a stabilizer with a medicine that is 100% crystalline.Depending on the kind of medication, there are two types of nanocrystalcreation processes: top- down and bottom-up. Nanoparticles can be made from both organic and inorganic materials. Drug crystals that are measured in nanometers and stabilized by a thin coating of surfactant are produced by nanocrystals, which are minuscule groups of atoms.Nowadays, nanocrystals can be made inthree mainways: "bottomup,""topdown,"and "bottomup"withspraydrying.Theoral nanocrystal-based drugs that are now approved are mostly used to treat conditions unrelated to cancer.

Keyword: Nanocrystalisation, bottom up, topdown, medicinal product

I. INTRODUCTION:

In the pharmaceutical sciences, ensuring the medications dissolve well in water is one of the most difficult problems. This issue is made more difficult by the fact that many approved medications and may be novel medications cannot dissolve well in water. The about 70% of currently in development medications are classified as class II by the Biopharmaceutics Classification System(BCS). These medications cannot dissolve readily in the body because of their sufficient solubility. Because, they are absorbed more slowly, which may result in poorer distributionthroughoutthe bodyand decreased effectiveness. It is more difficult to get the proper dosage of these medications for treatment because of their sluggish rate of dissolution. This demonstrates how crucial it is to address solubility issues when producing medications .[1] The researchers have explored methods to improve poorly soluble drug delivery, such as using co-solvents, salts, prodrugs, co-crystals, and cyclohexatriene complexes. Nanoparticles, especially lipid-based carriers, have gained attention for hydrophobic drugs but face challenges like low drug loading (5-30%), stability Issues, and solvent use. Nanocrystals (<1 μm) offer a promising alternative, with high drug loading and improved delivery efficiency due to their pure crystalline structure and stabilizer coating.[2] The nanocrystals can be made easily weing known methods without needing the costly equipment, nanocrystals, in contrast to larger-sized materials, demonstrate an increased surface are and apparent solubility, which in tumimproves the bioavailabilityand dissolution rate of weakly water-soluble medicinal compounds.

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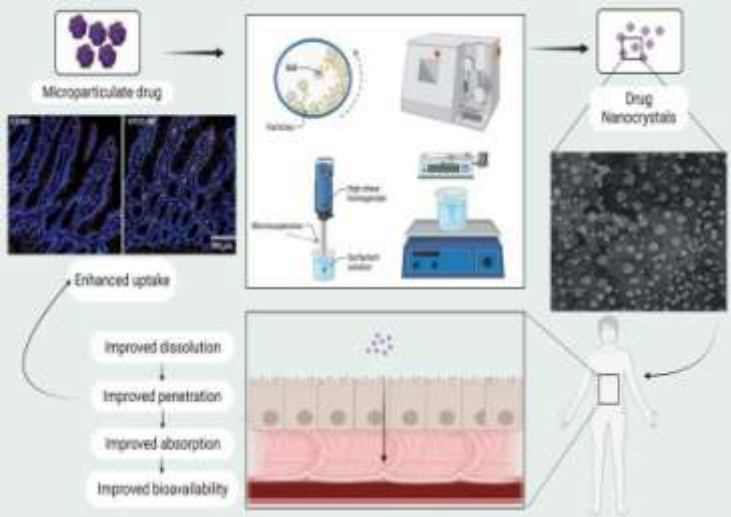

Fig01:NanocrystalinDrug development

Nanocrystals (NCs) offer advantages over lipid or polymeric carriers, delivering 100% drug content without extra materials. They are stable, pH-neutral, solvent-free, and scalable, making them ideal for hydrophobic drug delivery.These methods for creating nanocrystals can be divided into two categories based on the initial materials is top-down and bottom-up. High-pressure homogenization, microfluidization, and wet milling are examples of top-down techniques that reduce bigger materials into tiny nanocrystals. In contrast to the final nanoparticles (NPs), the initial material is composed of bigger solid particles, and mechanical procedures are the main method used to reduce particle size. On the other hand, bottom-up processes start with the creation of molecules. Cryogenic solvent evaporation, spraydrying, and electro sprayingare several techniques for evaporating solvents. This categorization also includes anti-solvent techniques, which include liquid anti-solvent and supercritical antisolvent techniques, among others. There are several advancements in targeted delivery of nanocrystals in progress, application in medical settings. Rapamune, the first medication based on nanocrystals, was introduced by Wyeth Pharmaceuticals in 2000. It is utilized as an immunosuppressant, however because it is poorly soluble, Rapamune® was developed. Utilizing the pearl mill method, and in contrast to ordinary sirolimus. It showed the 21% improvement in how much of the drug is absorbed when taken by mouth. Later, in 2003, Merck received approval for Emend®, a medication that helps prevent the nausea and vomiting but can not absorb very well in the stomach. [3] Nanocrystal formulations improved fenofibrate bioavailability by 9%, unaffected by food intake. Triglide®, approved in 2005 bySkye Pharma, uses high- pressure homogenization (HPH) and offers similar benefits to Tricor®. It shows consistent absorption and better intestinal adhesion in both fed and fasted states. Currently, it is marketed by the Sciele Pharma Inc.[4]

This review highlights nanocrystal manufacturing, their therapeutic applications, and the regulatory processes for Pending approvals.

Characterization of Nanocrystals:[5]

Nanocrystals creating the effective formulations requires selecting suitable excipients and thoroughout testing to ensure optimalperformance. The next sections outline keyevaluation methods.

1. SolidStateProperties
2. ThermalAnalysis
3. DiffractionofX-rays(XRD)
4. FT-IRResearch
5. SpectroscopyusingRaman
6. SizeDistributionandParticleSize
7. ShapeandMorphologyofParticles
8. SurfaceChargeofParticles
9. DissolutionofNanoparticles
10. Permeationstudy

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1. Solidstateproperties:

The quality of solid state of nanocrystals such as crystal structure, presence of solvents (especially water), and level of crystallinity is affect their solubility and how quickly they dissolve.It isdeterminethecharacteristicsofnanocrystalsisessential.Althoughlessstableor amorphous forms can improve solubility and bioavailability, they are rarely utilized.

Different methodsandconditionsusedto makenanocrystalsaffect thesolid formthat results. Additionally, environmental conditions influence which form is most stable. For instance, hydrate forms are less soluble in water-based environments because they are often morestable there. Therefore, during stability tests under various settings, the possibilityor reasons causing the aforementioned conversionshould be thoroughlyexamined whether the medicine is vulnerable to hydrate production. The solid-state form of nanocrystals is commonly analyzed using the X-raydiffraction, thermalanalysis, and vibrationalspectroscopy(infrared and Raman).[6]

2. ThermalAnalysis:

Drug nanocrystals'thermal characteristics and crystallinity, as well as their interactions with excipients,areexaminedusingdifferentialscanningCalorimetry(DSC)forpolymorphic medication and detectionof amorphous material using techniques like high-pressure homogenization is essential. DSC uses either heat flux or power-compensated procedures to test pure medicines, mixes, and final formulations.[7]

The thermal equivalent of Ohm's law, however, determines the resulting heat flow since the sample's heat capacity (Cp) would cause a temperature difference between the sample and reference pans, which isdetected byarea thermocouples: "sample heat flow" isdenoted byq, "temperature difference between sample and reference" by T, and "resistance of thermoelectricdisk" byRinthe formulaq= AT/R.[8]ThereferenceandsamplepansDifferent furnaces, each with its own heating, are used to store power- compensated DSC .[9]

The sample and reference pan temperatures are kept at the same level in power-compensated DSC, the power difference is recorded. The Kocbek et al. found ibuprofen nanosuspension withPoloxamer188showedeutecticmeltingat39.4°C andexcesscomponentmeltingat 56.8 °C. Similarly, DTA of SKLB610 revealed melting peaks at 155.7 °C and 132-133 °C, whichbecame lessdistinct innanosuspensionsdueto non-crystalline surfaces formed during preparation.[10]

3. DiffractionofX-rays (XRD):

The diffraction of X-rays (XRD) is used to confirm the crystallinity of drugs after they are turned into nanocrystals, as eachsubstance produces a unique diffractionpattern. Inthe study by Koneti et al., two methods for making glipizide nanosuspensions were compared the top- down (high-speed milling) and bottom-up (liquid antisolvent precipitation). XRD showedthat the crystallinity ofglipizide was preserved in both methods, with minimal changes in the diffraction peaks, though there was a slight decrease in intensity after spraydrying at high milling speeds.[11]

4. FTIR Research:

The chemical characteristics of a medicine and its interactions with excipients are assessed with the aid of FT-IR investigations. By comparing the infrared peaks of pure curcumin and the dry powder, Liandong et al. discovered that wet-milling and spray- drying curcumin nanocrystals for lung administration did not change their chemical structure. [12]

5. Spectroscopyusingraman:

A method based on the inelastic scattering of monochromatic laser light is called raman spectroscopy.Whenasampleisincontactwithphotons, theirfrequencyshiftsduetothe "Raman Effect," revealing information about molecular vibrations, rotations, and low- frequency transitions.Waard and associates created a technique for producing small drug crystals known as "controlled crystallization during freeze drying" (CCDF). Fenofibrate, a solvent, and a matrix material were combined, and the mixture was then freeze-dried. Therate at which the crystals froze determined their size. The freezing and crystallization processes were crucial in establishing crystal size, they discovered using Raman Spectroscopy. [13]

6. SizeDistributionandparticle size:

The size and size distribution are crucial in nanosuspensions, influencing stability, solubility, and clinical effectiveness.smaller particles increase surface energy, which may cause

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aggregation.a popular technique for determining particle size is dynamic light scattering (DLS), delivering quick, accurate results for particles under 6 microns. It also provides the polydispersity index (PI), where lower values indicate better stability. Optical microscopy is good for visualizing particles but inefficient for large-scale analysis, while laser diffraction (LD) offers a wide size range (0.05-2000 µm) and can analyze both large particles and nanoparticles, with a practical lower limit of around 400 nm.[14]

7. ShapeandMorphologyofparticles:

TEM and SEM are used the analyze nanocrystalshapes. TEM requires liquid samples, while SEM works with dried powders. Drying can cause agglomeration, but protectants like mannitolhelpreduce thissomeagglomerationisacceptable iftheparticlesizeremains within range and can re-disperse easily.[15]Using Atomic Force Microscopy (AFM), probucol nanocrystals combined withsodiumdodecyl sulphate (SDS) and polyvinylpyrrolidone (PVP) in water were investigated. The medication was encircled by PVP and SDS in a core-shell configuration created by the nanocrystals. AFM showed that the surface of the probucol particles with PVP K17 was stratified, whereas the particles with PVP K12 were not. These variations pertain to the creation of the PVP-SDS complex on the particles and aid in the explanation of the formation of nanoparticles as well as their possible absorption into the body. [16]

8. ParticleSurfaceCharge:

The surface charge of particles, measured as zeta potential, influences nanosuspension stability. Higher charge leads to greater electrostatic repulsion and improved stability. Zeta potential is determined through electrophoretic mobility or colloid titration. The dissociation offunctionalgroups,orthepH-dependent Nernstpotential,givesparticlesan intrinsic surface charge. Electrophoresis is used to quantify zeta potential, and Doppler shift and a field strength of 20 V/cm are used to determine particle velocity. The Helmholtz-Smoluchowski equation which can be simplified as multiplying mobility by 12.8 at 25°C, is used to convert the electrophoretic mobility to zeta potential.

9. DissolutionofNanocrystals:ApparentSolubilityandSupersaturatedState:

Thermodynamic solubility refers to the solubility of the most stable crystalline form at specific conditions while nanosized particles or amorphous forms can exhibit higher solubility, knownas kinetic or apparent solubility. This enhanced solubility can lead to super saturation, known as the "spring effect." Ige et al. found that fenofibrate nanocrystals (460 nm) had significantly higher solubility than the bulk drug (80 µm) in sodium dodecylsulphate solutions. [17] Using NMR spectroscopy, Ueda et al. investigated super saturation in the amorphous and nanocrystalline forms of carbamazepine. They discovered that for 50 hours, the concentration of nanocrystalline carbamazepine remained constant, stabilizing the solutionandavoidingsignificant precipitates. Theamorphousform,ontheotherhand,started out with a higher concentration but rapidly decreased as it crystallized into bigger particles. The size of the nanocrystals was around 150 nm.[18]

10. PermeationStudy:

Drugs with limited solubility may benefit greatly from improved cutaneous bioavailability usingnanocrystal-baseddrugdelivery. Indeed, nanocrystalshavetheabilitytobemoresticky totheskininadditionto havinghigher saturationsolubilityanddissolutionrate, whichmakes dermal distribution easier.[19]Increased concentration gradients or slow-release nanocrystals (700 nm) can be used to deliver drugs to the skin. Additionally, by improving solubility and retention, nanocrystals enhance the administration of eye drugs. Drug-stabilizer interactions, carrier surface, and particle size are important factors for poorly soluble medications; non- ionic surfactants are favored for formulations intended for the eyes.[20]

Pharmaceuticalapplicationsofnanocrystalsindrugdelivery:[21,22,23]

1. Parentaladministration
2. Peroraladministration
3. Pulmonarydrug delivery
4. Targetdrugdelivery
5. Dermaldrugdelivery

1. Parenteraladministration:

In nanosuspensions, drug nanocrystals can be given through various injection routes, including directlyinto joints (intra-articular), intothe abdomen(intraperitoneal),orinto veins (intravenous). These nanosuspensions can make injected drugs work better. For example, a nanosuspension ofthe anti-leprosydrug clofazimine,

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which doesn't dissolve well in water, is more stable and effective than clofazimine in a liposomal form.

2. Peroraladministration:

Making drugs into nanosized particles greatly increases their absorption when taken by mouth, which improves their effectiveness. Liquid nanosuspensions can be directly used in forms like tablets or hard gelatin capsules with small pellets.

3. Pulmonarydrugdelivery:

Water-based nanocrystals Both mechanical and ultrasonic nebulizers can be used for lung delivery. Because there are numerous small particles rather than a few micro particles, the dispersion can have a high concentration; all aerosol droplets contain medication nanocrystals.Budesonide, inadequatewatersolublecorticosteroid,whichhasbeeneffectively made as a nanosuspension and is used to treat lung infections using nebulization.

4. Targetdrugdelivery:

Drugscanbedeliveredspecificallyto particularbodilyparts using nanocrystals.Forinstance, a modified nanosuspension of the medicationbuparvaquone, which adheres to mucus and targets the organism, was used to treat cryptosporidiosis, an infection brought on by Cryptosporidium parvum. Similarly, ratherthan employing a stealth liposome, a nanosuspension of the medication amphotericin B can more successfully target lung infections such as pulmonary aspergillosis.

5. Dermal Drug Delivery:

Dermal nanosuspensions are helpful in situations where conventional formulations are ineffective. The product and skin have a greater concentration difference thanks to drug nanocrystals, which increases saturation and enhances skin absorption. Using positively charged polymers to stabilize the nanocrystals can enhance this effect even more since the medication adheres more readily to the negatively charged outer skin layer due to their positive charge.

Advantagesofnanocrystals:[24]

Enhanced Dissolution:

Asignificant benefit ofnanocrystals is their increased rate ofdisintegration. The surface area grove as the particle size decreases (Figure 2), which raises the dissolving velocity. Rapid drug diffusion from the particle surface to the bulk results from the lower thickness at the boundary caused by the higher surface curvature of small particles relative to large particles.[25]

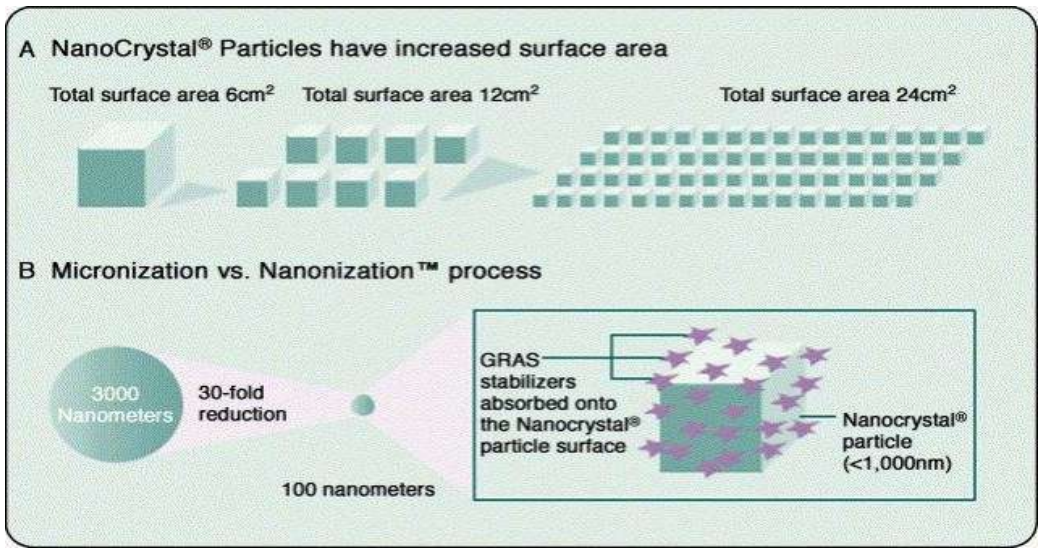

Figure 2: Schematic diagram of enhancement of surface area by nanonization (left) and nanocrystal particle (right)

Enhanced Solubility:

In simple terms, increasing saturation solubility is a unique feature of drug nanocrystals. Normally, a drug's saturation solubility depends on the temperature and the type of solvent used, especially when the drug particles are in the

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micrometer range. However, when the particle size is reduced to the nanometer scale, saturation solubility increases. This happens because smaller particles have a more curved surface, which raises the pressure on theparticle surface, allowing more drug molecules to dissolve. This increased dissolving ability results in higher solubility.[26]

EnhancedMucoadhesion:

One feature of medication nanocrystals that improves oral bioavailability is their increased adhesivenesstothebiologicalmucosa.Ahighconcentration gradientandanextendedretention period are caused by mucoadhesion at the absorption site. The mucoadhesive property of nanosuspensions is further strengthened by surface modification by the additionof mucoadhesive polymers, such as cationic polymers. For instance, buparvaquone nanosuspension made of chitosan and carbopol, two mucoadhesive polymers, has a longer retention period. [27]

Enhanced Safety :

Co-solvents or extremely high pH are needed to improve the solubility of poorly soluble medications. By formulating nanosuspension in aqueous dispersion, the negative consequences linked to cosolvent use are circumvented.[28]Cyclodextrin serves as a solubilizing ingredient in the injection of itraconazole, Sporanox.[29]One significant adverse effect that can be prevented with nanocrystal formulation is nephrotoxicity.

Disadvantagesofnanocrystals:[30,31]

1. Compression,deposition, andphysicalstabilitycanallbeproblematic.
2. Itrequirescarefulhandlingandtransportationbecauseitishefty.
3. Onecannotgetaconsistentandprecisedosage.

LimitationsofNanocrystals:[32]

1. Nanonization of medication size requires a lot of energy.
2. Stabilizerneed.
3. Notfor medicationswithpoortherapeuticindices.
4. Restrictedauthorityoverpublication.[33]

Nanocrystalpreparationmethods:[34]

Nanocrystalscanbepreparedusing "bottom-up,""top-down,""combined,"or"spray- Frying methods. Inthe bottom-up approach, particles formas the drug dissolves in a solvent and the solvent is removed. The top-down method, or "nanosizing," reduces larger particles via milling or homogenization and is most common. The combined method merges both approaches, while spray-drying simplifies and accelerates the process byspraying and drying the drug solution.[35]

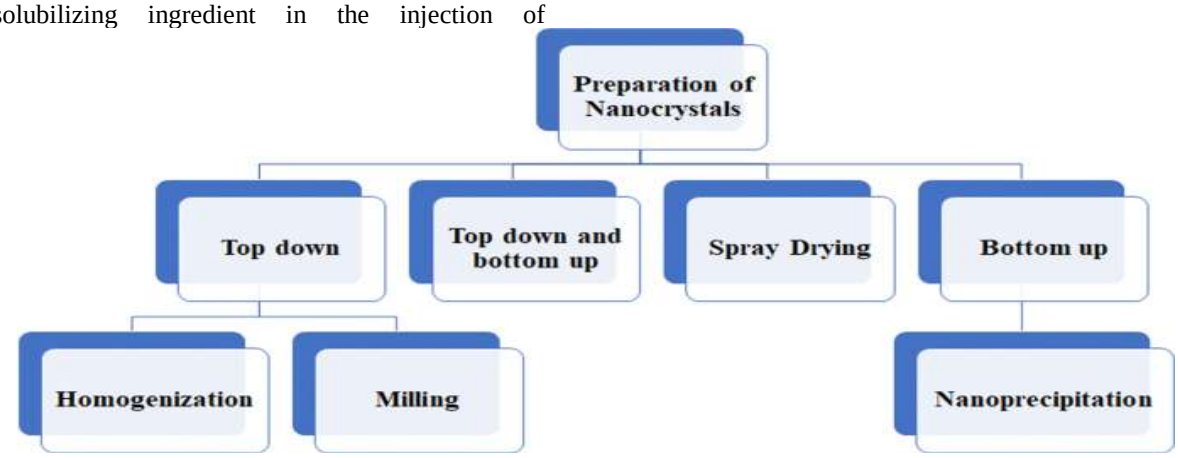

Fig03:PreparationMethodofNanocrystal

1. **Bottomup technology**

a) Nanoprecipitation.

2. **Topdowntechnology**

a) Milling,b)Homogenization.

3. **TopdownandBottomuptechnology**

4. **Spraydrying**
5. **OtherTechniquesusedfortheProductionofDrugNanocrystals**

a) Quickexpansionfromasolutionofliquefied gas:
b) SprayFreezinginto Liquid(SFL)

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1. Bottomup technology:

Inorderto precipitate nanocrystals, this process entails dissolving the active medication inan organic solvent and then adding it to a nonsolvent that is miscible with the solvent while stabilizers are present. Although the method is straightforward, inexpensive, and easily scalable, it requires careful controlof variables like temperature, solvent-to-nonsolvent ratio, drug concentration, viscosity, and stabilizer type in order to yield homogenous nanocrystals.[36]

a) Nanoprecipitation:

In order to stop the drug from growing to the micrometer range, stabilized nanocrystals are precipitated when the drug is dissolved in a solvent and then added to a nonsolvent. But for this to work, the medication must dissolve in at least one solvent, which presents difficulties for medications that are insoluble in bothorganic and aqueous solutions, which restricts their use.Aprotectivecolloid isaddedtoasurfactant-solutionat acertaintemperaturetocreatean O/W system in which the carotenoid localizes in the oily phase. Lyophilization and X-ray examinationshow thatapproximately90% ofthe carotenoid is inanamorphous condition. [37]

2. Top down technology:

Top-down technology uses various milling and homogenization techniques to apply dispersingstrategies. "Top-down"or"nanosizing"technologyismorecommontha n"Bottom up" technology. To put it another way, it is a process that reduces big crystalline particles to tiny ones. "Top down and bottom up" technology combines the two approaches. Either milling or homogenization can be used to implement top-down technology.

3. Milling methods:

Bead milling is used in the traditional Nanocrystal® technique to decrease the size of medication particles. In order to reduce size, milling beads, stabilizers, the medication, and a liquid medium are combined in a chamber where the movement of the beads produces shear pressures. Although protective bead coatings can lessen these problems, this low-energy approach, which uses beads made of materials like steel or ceramics, has drawbacks such as drug adhesion to the mill walls and bead wear introducing contaminants.

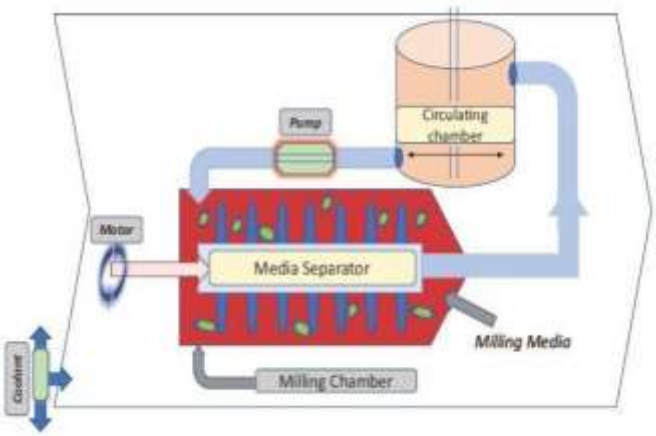

Fig4:Media melling equipment

The two method of milling include moving the container orthe beads with agitators; agitator mills work best for larger batches. Milling time can vary from 30 minutes to several days, depending on things like temperature, energy, mixture viscosity, drug hardness, amount of surfactant, and head size. This technique works and is found in four FDA-approved medications.[38]However, the need is to prevent the formulation from contamination. Media milling technology is shown in (Fig. 4).

a) Homogenizationmethod:

The Micro fluidizer is a jet streamthat uses DD-PTMtechnology. Two fluid streams that are homogenizers clash frontally at high speeds (up to 1000 m/sec). under 4000 bar of pressure. High shear forces, a turbulent flow, and particle

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collisions cause the particles to shrink to the manometer range. Areduction in size may also result from cavitations caused by the high pressure and rapid streaming velocity of the lipid. Stabilization with phospholipids or other stabilizers and surfactants is necessaryto stopthe particle size. For a suitable particle size reduction, 50 to 100 laborious passes are often required.

Piston-gap homogenizationin water(Dissocubes®):

High-pressure homogenization with piston gap homogenizers is another method for Creating drug nanocrystals. Withthistechnique, acylinder'spistongenerateshighpressure-upto 2000 bar-that pushes the suspension through a small opening. The pressure is maintained between 1500 and 150 bars, and the gap is typically 3 to 15micrometers wide.

the two main methods, DissoCubes® and NanoPure®, differ mainly based onthe temperature used and the liquid (water, in this case) that holds the nanocrystals. [39]

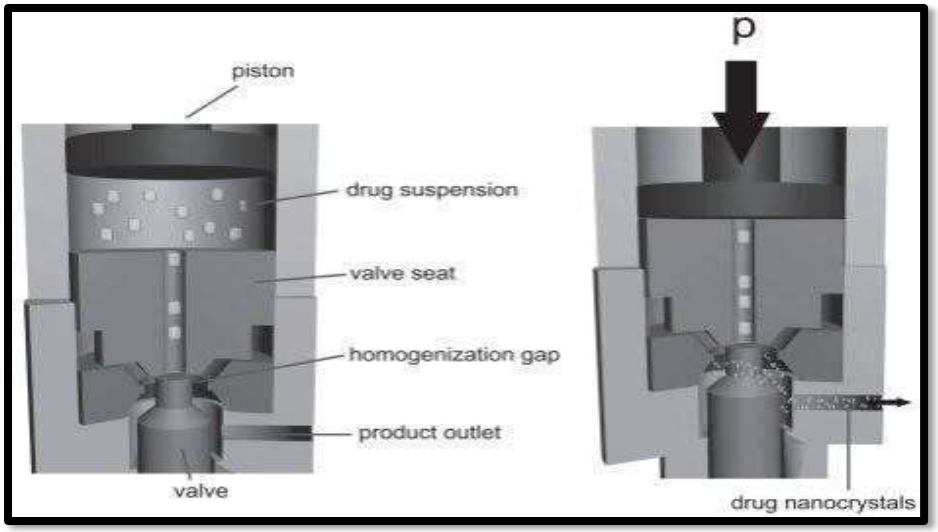

Figure 5: Basic principle of high pressure homogenization using a piston gap homogenizer

2.Topdownandbottomuptechnology:

Both approaches are merged in "top-down and bottom-up" technology. One product created with this combined strategy is Nano- Edge. Drugs that don't dissolve well in water can be treated with nano-edge technology. It performs best when the active components have high oil-water partition coefficients and melting points. Lipid emulsions, micro-precipitation, and direct homogenization are the three primary processes around which the technology is built. The medicine is initiallydissolved inasolventthatcancombinewithwatertoformasolution in the process of microprecipitation.The solution is then mixed with a second solvent to create a pre-suspension, which is then given energy to produce particles with an average effective particle size between 400 nm and 2 µ.

3) Spray Drying:

Spray drying is a method commonly used in dry solutions and suspensions, creating nanocrystals in the process. In this method, a liquid solution is sprayed from the top of a conicalor cylindricalchamber, whereit isdriedbyhot air flowing inthesamedirection. This drying process produces sphericalparticles. The solution is sprayed using an atomizer, which spinsquicklytospreadtheliquiddropletsbycentrifugal force.Thesolutionisfedintothe atomizer with a peristaltic pump at a steady flow rate, while air or nitrogen is applied at endless pressure through an outertube. The nozzle helps to spraythe solution into verysmall droplets, increasing the surface area and allowing it to dryquickly.It is possible to improve particle size, flow, and drying speed by adjusting important parameters like concentration, viscosity, temperature, and spray rate. Drugs like hydrocortisone and the COX-2 inhibitor BMS-347070 have been made more bioavailable and soluble by using this technique.

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Othertechnologies:[40,41]

a) Quick expansion from a solution of liquefied gas: This method works with materials that dissolve insupercriticalfluids, wherethesoluteexpandsquicklythroughanozzlea ndcan combine with carriers like PEG or oils to form capsules. It is quicker and perfect for medications that are sensitive to heat since it uses cavitation instead of dispersion media removal. Bycombiningwithisotonicwater-glycerolsolutions, it also facilitatesinjectable forms. With particle sizes of about 50 nm, Pharmasol's NANOPURE® XP technology produces translucent nanosuspensions and allows for scalable manufacturing in mild circumstances.

b) SprayFreezing into Liquid (SFL):The UniversityofTexas(Austin) createdand patented the SFL technology in 2003. The Dow Chemical Company (Midland, MI) subsequently brought it to market. Applying a drug-containing solution, emulsion, or suspension straight into a compressed gas (suchas CO2, propane, ethane, or helium) or anextremely cold liquid (such as argon, nitrogen, or hydrofluoroethers) is the process of this approach.

II. CONCLUSION:

Nanocrystalsareemergingasa groundbreaking innovationindrugdevelopment,offering improvements in the solubility, bioavailability, and effectiveness of poorlysoluble drugs. Despite some ongoing regulatory challenges, technological advancements and evolving regulatory frameworks are facilitating their broader adoption. As new formulation techniques continue to develop, nanocrystals are poised to enhance drug delivery, accelerate therapeutic effects, and minimize side effects, playing a crucialrole in shaping the future of pharmaceutical treatments.

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