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NANOPARTICLE TECHNOLOGY: FORMULATING POORLY WATER-SOLUBLE COMPOUNDS: A REVIEW

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ABSTRACT: One of the biggest challenges faced by pharmaceutical scientists is poor solubility and bioavailability of new chemical entities (NCEs). According to BCS classification; approximately 25% of all compounds are classified as highly soluble and permeable. Nearly 40% of the new chemical entities currently being discovered are lipophilic so poorly water soluble drugs. BCS Class II and Class IV have low solubility. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the *in -vivo* efficacy. A surprisingly large proportion of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These so-called 'brickdust' candidates can now be rescued by Nanonization. Formulating the poorly soluble compounds as pure drug nanoparticles is one of the newer drug-delivery strategies applied to this class of molecules. The present review deals in detail about the different techniques used for the improvement of the solubility and dissolution rate of poorly water soluble drugs with the use of nanoparticle as a drug delivery approach and characterization of nanoparticle.

INTRODUCTION: A large proportion of new chemical entities coming from drug discovery are water insoluble, and therefore poorly bioavailable. In biopharmaceutical classification system (BCS) **(Table.1)** Class II and Class IV have low solubility and low permeability. Class II drugs are now subdivided into class II a, where dissolution rate is the challenge, and Class II b, where apparent solubility of the drug molecule is low. [1, 3]

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TABLE.1: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

	High solubility	Low solubility
High permeability	Class 1	Class IIa: Dissolution rate limited Class IIb: Solubility limited
Low permeabilty	Class III	Class IV

Biopharmaceutical classification system

Drugs which are poorly soluble in water have a number of drawbacks such as high dosage administration frequency and the resultant

occurrence of side effects are Major issues associated with poorly water-soluble compounds shown below.

- Poor Bioavialability
- Inability to optimize lead compound selection based on efficacy and safety
- Fed/fasted variation in bioavailability
- Lack of dose-response proportionality
- Suboptimal dosing
- Use of harsh excipients, i.e., excessive use of cosolvents and other excipients
- Use of extreme basic or acidic conditions to enhance solubilization
- Uncontrollable precipitation after dosing
- Noncompliance by the patient, i.e., inconvenience of the dosage platform.

Furthermore, rate-limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs, Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. It is, important to improve the oral bioavailability of poorly water soluble drugs. Bioavialability is the availability of drug at the absorption site. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

Solubility and permeability is the deciding factor for *in-vivo* absorption of drug. Solubility of poorly water soluble drugs is explained by dissolution. Drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase.

The drugs which are poorly soluble in water because of low solubility also show slow dissolution rate. The rate of dissolution quantifies the speed of the dissolution process. The rate of dissolution can be often expressed by Noyes-Whitney Equation which described the quantitative analysis that correlated the amount of time it took to dissolve a drug from solid particles. [4, 5, 6]

Noyes-Whitney Equation:

The rate of dissolution (dM/dt)

$$\frac{dM}{dt} = \frac{DS\,(CS-Cb)}{h}$$

Where: M is amount of drug (material) dissolved (usually mg or mmol), t time (seconds) , D diffusion coefficient of drug (cm^2/s) ,S surface area (cm^2), h thickness of liquid film, Cs & Cb concentrations of drug at the surface of particle and the bulk medium respectively.

For absorption drug first dissolve in body fluids and then solution of drug transports through membrane. The transport of drug molecules through membrane occurs by diffusion. Similar to dissolution, the diffusion is described by FICK'S FIRST LAW: which states that the flux goes from regions of high concentration to low concentration, with a magnitude that is proportional to concentration gradient. [3, 1]

$$J = -D.\, d\Ø/dx$$

Where, J is flux (amount of substance), D coefficient of diffusivity, dØ change in concentration and dx change in position

Hence Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecule. The present review deals in detail about the different techniques used for the improvement of solubility and dissolution rate of poorly water soluble drugs with the use of nanoparticle as a drug delivery approach. According to Noyes-Whitney Equation there are two main possibilities of improving the dissolution rate of a drug by physical influence. First, D can be increased by micronizing the compounds or changing the surface properties, thus, increasing the wettability of particles. The second method is to increase the apparent Cs by changing to modifications with higher energetic states or by addition of solubility enhancing excipients. The solubility of poorly soluble drugs is increased by reducing particle size of the drug. [1]

TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly water soluble drugs. Some of the approaches to improve the solubility are shown in **Table 2**. [8, 9].

TABLE.2: DIFFERENT TECHNIQUES OF SOLUBILITY ENHANCEMENT

Physical modification	Chemical modification	Carrier/Delivery system
• Pro-drug	• Salts • Crystal engineering (polymorphs / co-crystals)	• Co-solvents • Polymeric systems • Cyclodextrins • Micelles • (Micro) Emulsions • SMEDDS • Liposomes • Micro-/Nanoparticales

Although all techniques mentioned above could enhance the solubility, the choice of the method will be based on its effectiveness as well as safety in terms of biocompatibility of excipients used. The solubility of poorly water soluble drugs is increased by reducing particle size of drug. The size of solid particle influences the solubility because as particle becomes smaller, surface area to volume ratio increases.

The larger surface area allows a greater interaction with solvent. When the total surface area of solute particle is increased, the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces increases its surface area and hence its rate of solution. By reducing the particle size, the increased surface area improves the dissolution properties of the drug.[8]

The present review deals in detail about the different techniques used for improvement of solubility and dissolution rate of poorly water soluble drugs with reducing the particle size of drug in nano range, that is by forming nanoparticle of them. The major goals in designing nanoparticles are to control particle size, surface properties to increase the solubility of poorly soluble drugs. [8, 9]

Nanotehnology is the study and use of materials and structures at the nanoscale level of approximately 100 Nanometers or less. New chemical entities have very low solubility there oral bioavailability and solubility is enhanced by Nanonisation. [10] Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm**.** The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. [11]

NANOTECHNOLOGY APPROACHES [11]

Nanoparticles are typically defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 micron in an external phase and Nano crystal is a crystalline material with dimensions in nanometers. Nanocrystalisation is defined as a way of redusing drug particals to the size range of 1-1000 Nanometers. According to the size range nanoparticals are categorized as shown if **Fig.1**

- Coarse Partical cover a range between 10000nm to 2500nm.
- Fine Partical are sized in range between 2500 to 100nm.
- Ultra Fine nanopartical are sized between 1 to 100nm.
- Nanoclusters are those which have at least one dimension between 1 to100nm and have a narrow size distribution.
- Nanopowders are agglomerates of ultrafine particle, nanoparticle or nanoclusters.

The major goals in designing nanoparticles are to control particle size, surface properties to increase the solubility of the poorly soluble drugs. [10]

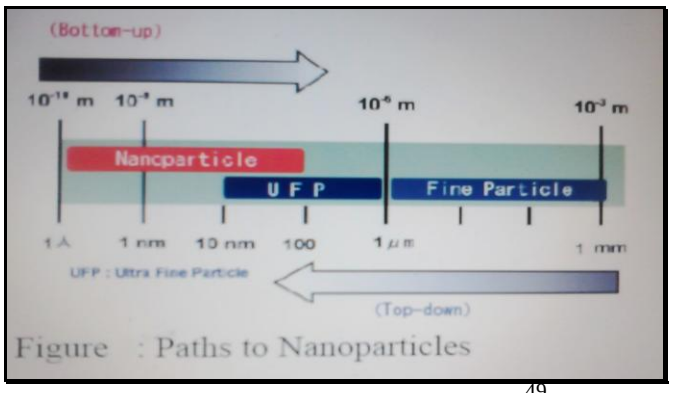


FIG.1: PATHS TO NANOPARTICLE [49]

Advantages of nanoparticles [11, 12]

1. Increase the stability of any volatile pharmaceutical agent, easily and cheaply fabricated in large quantities by a multitude of methods.

2. They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.

3. Deliver a higher concentration of pharmaceutical agent to a desired location.

4. Choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics. Polymeric Nanoparticles can be easily incorporated into other activities related to drug, such as tissue engineering.

METHODS OF PREPARING NANOPARTICLE [10, 11, 12]

There are various ways in which nanoparticles of poorly water-soluble molecules are generated. Nanoparticles are formed by following methodologies.

In bottom up methods

- Precipitation method
- Cryo-vaccum method

In top down method

- Milling
- High pressure homogenization

Top down and bottom up

Spray dying

"Bottom up" technology begins with the molecule; active drug substance is dissolved by adding an organic solvent, and then, solvent is removed by precipitation. "Top-down" technology applies dispersing methods by using different types of milling and homogenization techniques. "Topdown" technology is more popular than "Bottom up" technology; it is known as "nanosizing". In other words, it is a process which breaks down large crystalline particles into small pieces. In "top down and bottom up" technology, both methods are utilized together. Spray drying is also a method for preparing drug nanocrystals, which is faster and more practical compared to other methods. No matter what approach is taken to generate drug nanoparticles, in comparison to particulates greater than 1 micron, surface area is increased. [12, 13]

Bottom up technology

"Bottom up" technology relies on precipitation. The principle of this method is based on the dissolution of active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated.

Precipitation method [9, 15, 37]

Nanoprecipitation is also called solvent displacement method. It involves precipitation of a preformed polymer from an organic solution and diffusion of organic solvent in aqueous medium in the presence or absence of a surfactant.

In precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good. The solution with the drug is then injected into water, which acts as a bad solvent, at the time of injection; the water has to be stirred efficiently so that the substance will precipitate as Nano crystals **(Fig. 2)** Nanocrystals can be removed from the solution by filtering and then dried in air.

In Nanoprecipitation the polymer generally PLA, is used, this method is also called solvent displacement method. The solvent displacement technique allows the preparation of nanocapsules when a small volume of oil incorporated in organic phase. [16]

- It should be kept in mind that several parameters; such as stirring rate, temperature, solvent/nonsolvent rate, drug concentration, viscosity, type of solvent and stabilizer should be controlled in order to obtain homogenous nanocrystals by this technique.

Basic advantage of precipitation technique is that it is simple and has a low cost. Also, scale up is

simple. This method has numerous limitations**;** it is very difficult to control nucleation and crystal growth to obtain a narrow size distribution. Often a metastable solid, usually amorphous, is formed which is converted to more stable crystalline form.[16]

- Furthermore, non-aqueous solvents utilized in the precipitation process must be reduced to toxicologically acceptable levels in the end product and due to the fact that many poorly soluble drugs are sparingly soluble not only in aqueous but also in organic media.

Considering these limitations, the "bottom up" techniques are not widely used for production of drug nanocrystals. Instead, "top down" technologies that include homogenization and milling techniques are more frequently used. [17, 18] Examples of products manufactured by the precipitation method are Hydrosols and Solids Nanomorph respectively.

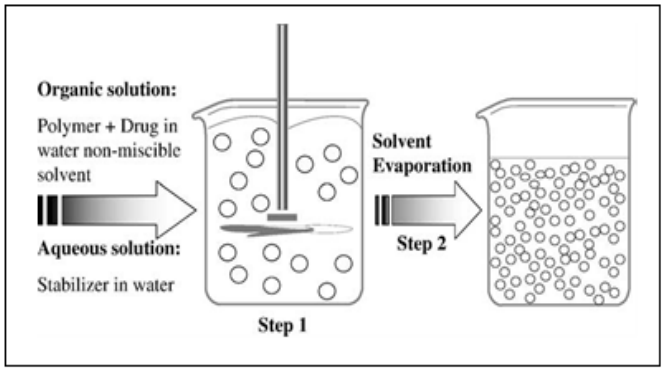


FIG.2: PRECIPITATION METHOD FOR PREPARING NANO CRYSTALS

Cryo-vaccum method

In this method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution**.** The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C). Rapid cooling causes a very fast rise in the degree of saturation based on decrease of solubility and development of ice crystals when the temperature drops below 0°C. This leads to a fast nucleation of dissolved substance at the edges of ice crystals. The solvent must be completely frozen before the vessel is removed from liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant -22°C and pressure is lowered to 10-2 m.bar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of particles produced, so as to remain crystalline. The method yields very pure nanocrystals and there is no need to use surfactants or harmful reagents. [20]

TOP DOWN METHOD

Milling [18, 21 22, 23 24, 25, 28]

Nano suspensions are produced by using high shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. Grinder chambers are made from stainless steel, porcelain or hard material. The milling media or grinding balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. For the purpose of making Nano size range particles the drug formulation is fed into mill containing small grinding balls/pearls. [33]

As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction. Planetary ball mill is one example of equipment that can be used to achieve a grind size below 0.1µm. [32-38]

Milling principles- There are two basic milling principles - either the milling medium is moved by an agitator or the complete container is moved in a complex direction leading to movement of milling media to generate shear forces required to fracture the drug crystals.[36,38]

Key property of grinding media [24]

- **Size** -Smaller the media particles, smaller the particle size of final product. At the same time, the grinding media particles should be substantially larger than the largest pieces of material to be ground.
- **Density** -the media should be denser than the material to be ground.it becomes a problem if the grinding media is less denser than the material.

- **Hardness** -The grinding media needs to be durable enough to grind the material, but where possible should not be so tough that it also wears down the tumbler at a fast pace.
- **Composition**-various grinding applications have special requirements. Some of these requirements are based on the fact that some of the grinding media will be in finished product. Others are based on how the media will react with the material being ground.[24]

- The **major drawbacks** of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5 μm. To overcome this contamination issue, the milling media are often coated. Or agate balls are frequently used in the pharmaceutical field as the possibility of such an interaction and contamination is minimized
- Another problem with milling process is the adherence of product to inner surface of mill (consisting mainly of the surface of milling media and the inner surface of milling chamber). The type of material that the balls are made of is very important since an interaction could take place between the material and drug substance.

Factors that effect milling performance [24, 26, 28, 31, 37]

- The milling time depends on many factors such as solid content, surfactant concentration, hardness, suspension viscosity, temperature, energy input and, the size of milling media. The milling time may vary from minutes to hours or days depending on particle size desired.
- The number of milling balls, amount of drug and stabilizer, milling time and speed, type of grinding chamber and temperature. In contrast with high pressure homogenization, it is a low energy technique.
- Grinder chambers are made from stainless steel, porcelain or hard material, and the balls are made from porcelain, glass, zirconium oxide, stainless steel, chromium, agate, or special polymer materials. The type of material that the balls are made of is very important since an interaction could take place between the material and the drug substance. This interaction can be reduced by using surface active agents or polymers.
- Another important factor is the size of balls. When the balls with small diameter are used, grinding time is extended but smaller particles are obtained. The mechanism of ball milling is that while grinding chamber is rotated, balls are rotated too, and at the end of this procedure, the particle size of active drug substance is reduced by mechanical energy. Thus, particle size of active drug substances can be adjusted by changing the diameter and number of balls.
- Rotational speed of grinding chamber is also very important. If the rotational speed is too low, balls cannot rotate effectively and grinding cannot be done efficiently. If rotational speed is very high, balls will remain at the edge of the grinding chamber due to centrifugal forces and grinding cannot be done effectively. Moreover, for efficient grinding the volume of the balls should be 30 % to 50 % of the grinding chamber.
- Increase in the temperatures locally inside the milling chamber may facilitate the growth of Particles

Dyno Mill. [24, 47, 49]

For dispersion and wet grinding in the micron to nano range dyno mill is generally used.

Features of dyno mill

1. Ideal for small scale production.
2. Available for continuous or discontinuous operations.
3. Ideal equipment for all type of product with the choice of widest possible range of material that come in contact with the product.
4. Easy to operate.

Working of Dyno mill [24, 47, 48, 49]

The milling chamber has a rotor fitted with disks that can be accelerated at the desired speed (500 – 5000 RPM). The rotation of disk accelerates /milling media radially. The product flows axially through the milling chamber where the shear forces

generated and/or forces generated during impaction of milling media with the drug provides the energy input to fracture the drug crystals into nanometer-sized particles. The temperature inside the milling chamber is controlled by circulating coolant through the outer jacket. **(Fig.3)**. The process can be performed either in a batch mode or in a recirculation mode. The milled product is subsequently separated from milling media using a separation system. The mechanism of milling is fairly complex and does not lend itself easily to rigorous theoretical analysis due to its dynamic nature. According to particle nature nanorods could be produced by fracture.

Smaller the grinding beads, higher is their number in a given grinding chamber volume. Higher the number of beads higher is the stress frequency. More grinding will occur and product of nano range is obtained.

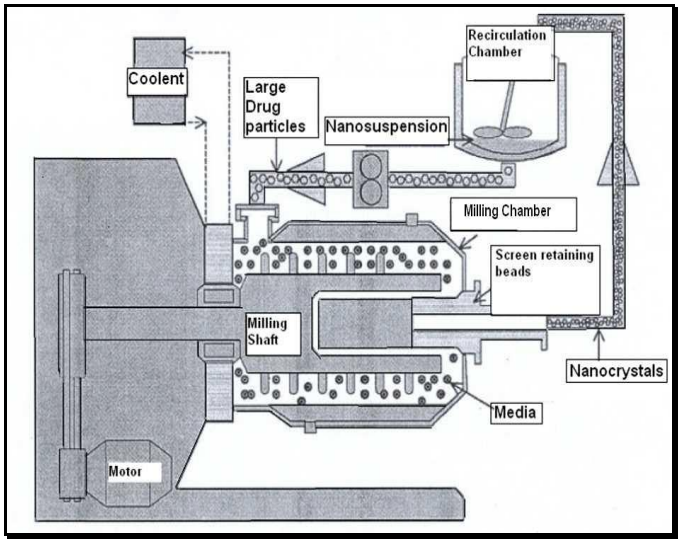


FIG. 3: SCHEMATIC OF WET BEAD MILLING PROCESS USED FOR PRODUCTION OF DRUG NANOPARTICLES

Guidelines about selection criteria for mill media: [24]

- Should be harder than the material to be ground.
- Should be denser than the material to be ground.
- Composition should not contaminate the product (Inert media for mineral industry).
- Should be competent by having a mechanical integrity.
- Make-up media size should be the smallest one required to grind the coarse particles.
- Should be cost-effective for the application.
- Should be easily separated from the finished product (i, e steel dust produced from non ferrous products), an alternative to separation is to use media of same material as product being ground. **(Fig.4)**

FIG. 4: DIFFERENT SIZES AND SHAPES OF MILL MEDIA

For the molabile and temperature sensitive materials porcelain or hard material beads of different size are available , low size beads generated heat by attrition which degrade the product and also heat causes fusion of nanoparticles which leads to increase in particle size thus low aqueous solubility. For aqueous solvent based suspension aluminium oxide and zirconium oxide beads should be used. For contamination sensitive products abrasion resistance highly cross-linked polystyrene resin beads should be used with small size range. Dyno mill is available in various series like DYNO-MILL ECM, DYNO-MILL KD shown in **Fig.5**.

FIG.5. DIFFERENT MODELS OF DYNO MIL

Homogenization [31, 32]

Homogenization involves the forcing of drug solution under pressure through a valve having a narrow aperture. In this case, the drug solution is made to pass through a small orifice that result in a reduction of static pressure below the boiling of water, which leads to boiling of water and formation of gas bubbles.

When the solution leaves the gap and normal air pressure is reached again, the bubbles implode and surrounding part containing drug particles rushes to the center and in the process collide, causing a reduction in particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on hardness of drug, the desired mean particle size and required homogeneity.

- The major advantage of high pressure homogenization over media milling is that it can be used for both diluted as well as concentrated solution and also allows aseptic production.
- To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling.

Hot homogenization: Hot homogenization is carried out at temperatures above the melting point. First disperse/dissolve drug in the melted lipid and then add this mixture to hot aqueous surfactant solution using stirring device. The obtained pre emulsion is homogenized at higher pressure to get hot nano product. Finally the above solution is cooled to room temperature. In most cases 3-5 homogenization cycles at 500-1500 bar are sufficient. Increasing the homogenization leads to an increase of particle size due to particle coalescence which occurs because of high kinetic energy of particles.

- The main drawback of this method is High temperature leads to degradation of active compound and Partitioning and hence loss of drug from the aqueous phase during homogenization.

Cold homogenization: Cold homogenization has been developed to overcome various problems associated with hot homogenization. First disperse/dissolve drug in the melted lipid and solidify the mixture using liquid nitrogen/dry ice. The solidified mixture is grinded to fine particles using powder mill and dispersed in a cold surfactant solution using stirrer. The obtained pre suspension is homogenized at higher pressure and at below room temperature to get nanoparticles.

- Compared to hot homogenization; larger particle sizes and a broader size distribution is typical of cold homogenized samples.
- Cold homogenization minimizes the thermal exposure of sample.

High pressure homogenization methods (Hot homogenization)

One of the methods used for size reduction is high-pressure homogenization.

The two - homogenization principles/homogenizer used is;

- Microfluidisation (Microfluidics, Inc.)
- Piston-gap homogenizers (e.g. APV Gaulin, Avestin, etc.)

Micro fluidisation for production of drug nanoparticles. [30]

Micro fluidisation works on a jet stream principle where the suspension is accelerated and passed at a high velocity through specially designed interaction chambers. Frontal collision of fluid streams under high pressures (up to 1700 bar) inside the

interaction chamber generates shear forces, particle collision, and cavitation forces necessary for particle size reduction. The Micro fluidizer processor keeps a constant feed stream that gets processed by a fixed geometry which produces high shear and impact necessary to break down larger particles. This process yields smaller particles with narrow particle size distribution with repeatability and scalability.

The interaction chamber's exterior and interior is either made of stainless steel, polycrystalline diamond (PCD) or aluminum oxide. The poly-crystalline diamond chambers typically have a lifetime 3 - 4 times longer than the aluminum oxide ceramic chambers.

- Single slotted interaction chambers are used for lab-scale manufacturing and multi-slotted chambers for commercial scale.
- Multi-slotted chambers comprise of multiple single slots in parallel for processing larger volumes of products.
- There are two types of interaction chambers: Y chamber is useful for liquid-liquid emulsions and finds application in preparing liposomes while Z-chamber is typically used for cell disruption and nanodispersion. A schematic representation of mechanism of particle size reduction in high pressure homogenizers is shown in **Fig.6**
- The selection of correct chamber depends upon the feed particle size, application, and amount of shear and impact required to carry out the operation.
- Increasing speed of homogenization in hot homogenization has been found to reduce the size of produced nanoparticles.[31]

Process parameters affecting particle size [21]

Studies on particle size reduction of a sparingly soluble drug (BCS class II) using the Micro fluidizer depends on various process parameters viz., number of homogenization cycles, homogenization pressure and, stabilizer concentration. Surfactant concentration also plays an important role in particle size reduction through particle stabilization by forming a thin layer around the newly formed surface of the particles. At constant homogenization pressure and homogenization cycles, particle size reduced with increase in surfactant concentration. [28]

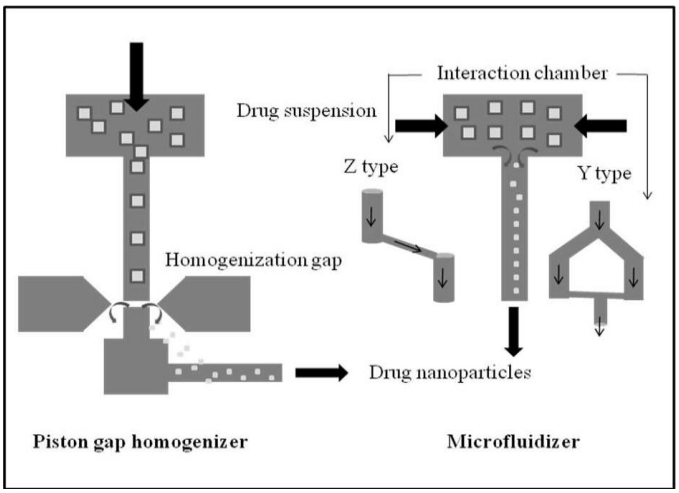


FIG. 6: SCHEMATIC REPRESENTATION OF MECHANISM OF PARTICLE SIZE REDUCTION IN HIGH PRESSURE HOMOGENIZERS

Piston-gap technologies

Using the micro fluidisation principle, an alternative technology based on piston-gap homogenizers was developed in the middle of 1990's for production of drug nanoparticles. Homogenization can be performed in water (DISSOCUBES) or alternatively in non-aqueous media or water reduced media (NANOPURE).

Disso cubes technology employs piston-gap homogenizers in which drug powder is dispersed in an aqueous surfactant solution and subsequently forced by a piston through tiny homogenization gap (5 μm - 20 μm) depending upon the viscosity of suspension and applied pressure at a very high pressure (up to 4000 bar). Prior to entering the gap, the suspension is contained in a cylinder with a relatively large diameter compared to the width of following gap. [34]

The resulting high streaming velocity of suspension causes formation and implosion of bubbles also known as cavitation which results in generation of shockwaves. **Fig.6** The drug particle gets reduced by these high shear forces, turbulent flow and powerful shockwaves. Another approach viz., Nanopure technology is useful for particle size reduction of thermolabile drugs because it uses low vapor pressure dispersion media for homogenization that helps in processing at low

temperatures due to very little cavitation in homogenization gap.[31,32,33,34,35]

In addition, there is also a combination process of precipitation followed by a second high-energy homogenization step (NANOEDGE).

- The major limitation of this method is that nanoparticulate dispersion of low solid content (usually < 10% w/v) is produced that may be difficult for conversion to solid intermediates required for capsule filling or tableting.[42]

Top down and bottom up technology

In "top down and bottom up" technology, both methods are used together. NanoEdge is a product obtained by such a combination technology. As can be inferred, precipitation is followed by high pressure homogenization in this technology

Spray Drying [11, 12, 37]

One of the preparation methods of nanocrystals is spray drying. This method is usually used for drying of solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom, dried in the same direction by hot air and spherical particles are obtained. Spraying is made with an atomizer which rapidly rotates and provides scattering of the solution due to centrifugal effect. The solution, at a certain flow rate, is sent to the inner tube with a peristaltic pump, nitrogen or air at a constant pressure is sent to the outer tube. Spraying is provided by a nozzle. Droplets of solution become very small due to spraying; therefore, surface area of drying matter increases leading to fast drying.

- Concentration, viscosity, temperature and spray rate of solution can be adjusted and particle size, fluidity and drying speed can be optimized.
- The dissolution rate and bioavailability of several drugs, including hydrocortisone, COX-2 Inhibitor were improved utilizing this method

POLYMERS USED IN PREPARATION OF NANOPARTICLES

The polymers should be compatible with the body in terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible. The most commonly used natural and synthetic polymers are shown in table: 3 [13]

TABLE.3: COMMONLY USED NATURAL AND SYNTHETIC POLYMERS

Natural polymers	Synthetic polymer
• Chitosan • Gelatin • Sodium alginate • Albumin	• Polylactides(PLA) • Polyglycolides(PGA) • Poly(lactideco-glycolides) (PLGA) • Polyanhydrides • Polyorthoesters • Polycyanoacrylates • Polycaprolactone • Poly glutamic acid • Poly malic acid • Poly(N-vinyl pyrrolidone) • Poly(methyl methacrylate) • Poly(vinyl alcohol) • Poly(acrylic acid) • Poly acryl amide • Poly(ethylene glycol) • Poly(met acrylic acid)

Selection of stabilizers for nanocrystal preparation

Selection of stabilizers is very important in nanocrystal formulations, because the type and concentration of stabilizer affect the final size of particles, and also stabilizers prevent nanocrystals from reaggregating. In the absence of appropriate stabilizers, the high surface energy of nanometer sized particles would lead to agglomeration or aggregation of drug crystals. The concentration of polymeric stabilizers can range from 1 – 10% w/v and the concentration of surfactants is generally < 1 % w/v. If required other excipients such as buffers,

salts and diluents like sugar can be added to the dispersion to enhance stability and aid further processing. [38, 44]

- A phenomenon called Ostwald ripening results from uncontrolled precipitation or crystallization of active substances leading to particle size growth following stabilization, this can be prevented and reduced by controlling a number of formulation parameters such as particle size, particle size distribution, solid content ,choice of stabilizer and a fluid phase with minimal potential to solubilize the poorly water soluble compound. [43,45]

Polymers or surface active agents exert their effect by covering the surface of drug nanocrystals and providing stabilization by creating a steric barrier. At the nano size, forces between particles due to dispersion or van der Waals forces come into play. Nanosized particles with a high surface area have high surface free energy (ΔG). Thus, particles tend to agglomerate in order to decrease surface free energy leading to an increase in particle size and reduction in surface area. Therefore, a stabilizer leads to a decrease in ΔG by decreasing the interfacial tension **γs/l** shown in equation

$$\Delta G = \Delta A \bullet \gamma s/l$$

γs/l- interfacial tension between the surfaces of solid and surrounding liquid phase (joule/m^2)
ΔG-change in surface free energy (joule)
ΔA- change in surface area (m^2)

An acceptable stabilizer should be [45]

1. Safe for the intended route of administration.
2. Stabilizer must have properties that allow it to properly wet the surface of poorly water-soluble compounds.
3. Stabilizer should possess properties so as to impart steric and/or ionic stabilization to the surface of nanoparticles. It should be emphasized that surface stabilization does not necessarily involve chemical grafting of the surface stabilizer to the molecule.
4. Stabilization is typically driven by mere adsorption of the stabilizer to the surface of poorly water-soluble compound.

CHARACTERIZATION OF DRUG NANOPARTICLES [9, 21, 15, 46]

There are various techniques used for characterization of drug nanoparticles. There is no single method that can be selected as the "best" for analysis. Most often the method is chosen to balance the restriction on sample size, information required, time constraints and cost of analysis. Following methods are used commonly for characterization of drug nanoparticles.

Particle size and size distribution

The characterization of particle size of nanoparticles is done to obtain information about its average size, size distribution and change upon storage (e.g. crystal growth and/or agglomeration). Particle size distribution of drug nanoparticles can be measured using the following techniques.

Spectroscopy

The appropriate method used to evaluate particle size distribution of submicron particle is photon correlation spectroscopy (PCS). In PCS or dynamic light scattering analyses scattered laser light from particles diffusing in a low viscosity dispersion medium (e.g. water). PCS analyze the fluctuation in velocity of the scattered light rather than the total intensity of scattered light. The detected intensity signals (photons) are used to measure the correlation function. The diffusion coefficient D of particles is obtained from the decay of this correlation function by Stokes- Einstein equation.

$$D = \mu\, kBT$$

Where, D is diffusion constant, μ the "mobility", or ratio of particle's terminal drift velocity to an applied force, μ, v_d / F, k_B Boltzmann's constant, T absolute temperature,

Applying Stokes- Einstein equation, the mean particle size (called z-average) can be calculated. In addition, a polydispersity index (PI) is obtained as a measure for the width of distribution. The PI value is 0 in case particles are monodisperse.

In case of narrow distribution, the PI values vary between 0.10 – 0.20, values of 0.5 and higher indicate a very broad distribution (polydispersity). From the values of z-average and PI, even small increases in size of drug nanoparticles can be evaluated. The extent of increase in particle size upon storage is a measure of instability. Therefore,

PCS is considered as a sensitive instrument to detect instabilities during long-term storage. [9, 10, 39]

Laser Diffraction

The instrument is used for quantifying the amount of microparticles present, which is not possible using PCS. LD analyses the Fraunhofer diffraction in a laser beam. The first instruments were based patterns generated by particles on Fraunhofer theory which is applicable for particle sizes 10 times larger than the wavelength of light used for generating diffraction pattern.

For particle less than 6.3 μm (in case of using a helium neon laser, wavelength 632.8 nm) in size, the Mie theory is used to obtain the correct particle size distribution. The Mie theory requires knowledge of actual refractive index of particles and their imaginary refractive index (absorbance of the light by the particles). Unfortunately, for most of pharmaceutical solids the refractive index is unknown. However, laser diffractometry is frequently used as a preferred characterization method for nanoparticles because of its "simplicity.

Microscopy

Microscopy based techniques can be used to study a wide range of materials with a broad distribution of particle sizes, ranging from nanometer to millimeter scale. Instruments used for microscopy based techniques include optical light microscopes, scanning electron microscopes (SEM) transmission electron microscopes (TEM) and atomic force microscopes (AFM). The choice of instrument for evaluation is determined by the size range of the particles being studied, magnification, and resolution.

However, the cost of analysis is also observed to increase as the size of particles decreases due to requirements for higher magnification, improved resolution, greater reliability and, reproducibility. The cost of size analysis also depends upon the system being studied, as it dictates the technique used for specimen preparation and image analysis.

Optical microscopes tend to be more affordable and comparatively easier to operate and maintain than electron microscopes but have limited magnification and resolution.[40]

Thermoscopy (Hot Stage Microscopy):

HSM of pure drug, solid dispersions and for nanoparticles are conducted using Mettler Toledo hot stage microscope of 200 magnification using IM50 software. A small amount (2-4 mg) 0f sample is placed on a glass slide with a cover glass and heated at 3°C/min. Changes in sample morphology are noted as a function of temperature.

Solid-state properties

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is used to determine the crystallinity of drug nanoparticles by measuring its glass transition temperature, melting point and their associated enthalpies. This method along with X-ray powder diffraction (XRPD) described below is used to determine the extent to which multiple phases exist in the interior and their interaction following the milling process.

X-ray powder diffraction (XRPD)

X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions.

X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays generated by a cathode ray tube are filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interference obtained is evaluated using Bragg's Law to determine various characteristics of crystal or polycrystalline material.[41]

Saturation solubility and dissolution velocity

The nanonization increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. [42]

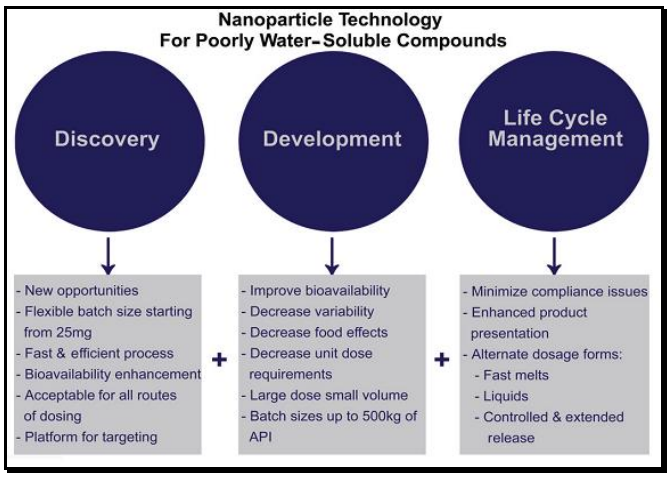
NANOPARTICLES:

IMPROVED PERFORMANCE

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon solubility of drug molecules. Solubility is one of the important

parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.

NANOPARTICLES: THE BIOLOGICAL BENEFITS [13]



The poor bioavailability of poorly water-soluble molecules that are not permeation-rate limited can be attributed to dissolution-rate kinetics. The dissolution rate is directly proportional to surface area of drug, according to the Noyes-Whitney model for dissolution kinetics. Drug crystals reduced in size from 10 microns to 100-nm particles generate a 100-fold increase in surface-area-to-volume ratio.

This increase in surface area has a profound impact on bioavailability of the molecule. The nanotechnology can be proved as a gift for the poorly water soluble drugs can be easily formulated into nanoparticles. One of the critical problems associated with poorly soluble drugs as they have low bioavailability. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability.

Nanonization not only solves the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Current marketed pharmaceutical products utilizing nanoparticle formation are described in **Table. 4**.

TABLE.4: LIST OF SOME MARKETED PRODUCTS

Trade name	Active Salt	Category	Company	Administration
Rapamune	Sirolimus	Immunosuppressant	Elan,Wyeth	Oral
Abelect	amphotericin B	Fungal infection	Enzon	Intravenous
Emend	Aprepitant	Antiemetic	Merck	Intravenous
Epaxal	Liposomal IRIV vaccine	Hepatitis A	Berna Biotech	Intramuscular
Megace	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	Oral
Estrasorb	Micellular estradiol	Menopausal therapy	Novavax	Topical
Triglide	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical	Oral
Pegasys	PEG–a-interferon 2a	Hepatitis B, Hepatitis C	Nektar, Hoffmann-La Roche	Subcutaneous
Renagel	Poly(allylamine hydrochloride)	End-stage renal disease	Genzyme	Oral
Tricor	Fenofibrate	Treatment of hypercholesterolemia	Elan, Abbott	Oral

FUTURE SCOPE OF NANOPARTICLES

Nanoparticle–formulation technologies have provided the pharmaceutical industry with new strategies for solving the problem of poorly soluble molecule._Nanoparticle formulation can be post processed into various types of patient friendly dosage forms that provide maximal drug exposure and bioavailability.

Nanoparticle formulation strategies provide a mean to incorporate old drug into a new drug delivery platform. For future drug –nanoparticle unfolds many new approaches for drug targeting and permeation enhancement of different classes of drugs. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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