’’ Exploring pharmaceutical Nanocrystals for enhanced drug delivery ’’

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Topics:

What is the nanocrystal technology?

Benefits of pharmaceutical nanocrystals

Methods for preparation

Limitation …!

Factors affecting on preparation

pharmaceutical nanocrystals and their advantages:

Drug nanocrystals are insoluble drug particles that form inhomogeneous water dispersions under the effect of stabilizer (as surfactants or polymers)

Drug nanocrystal technology has been widely investigated as a method for overcome the problems of low drug solubility and increasing the bioavailability of insoluble drugs, due to their submicron particle size and unique physicochemical properties.

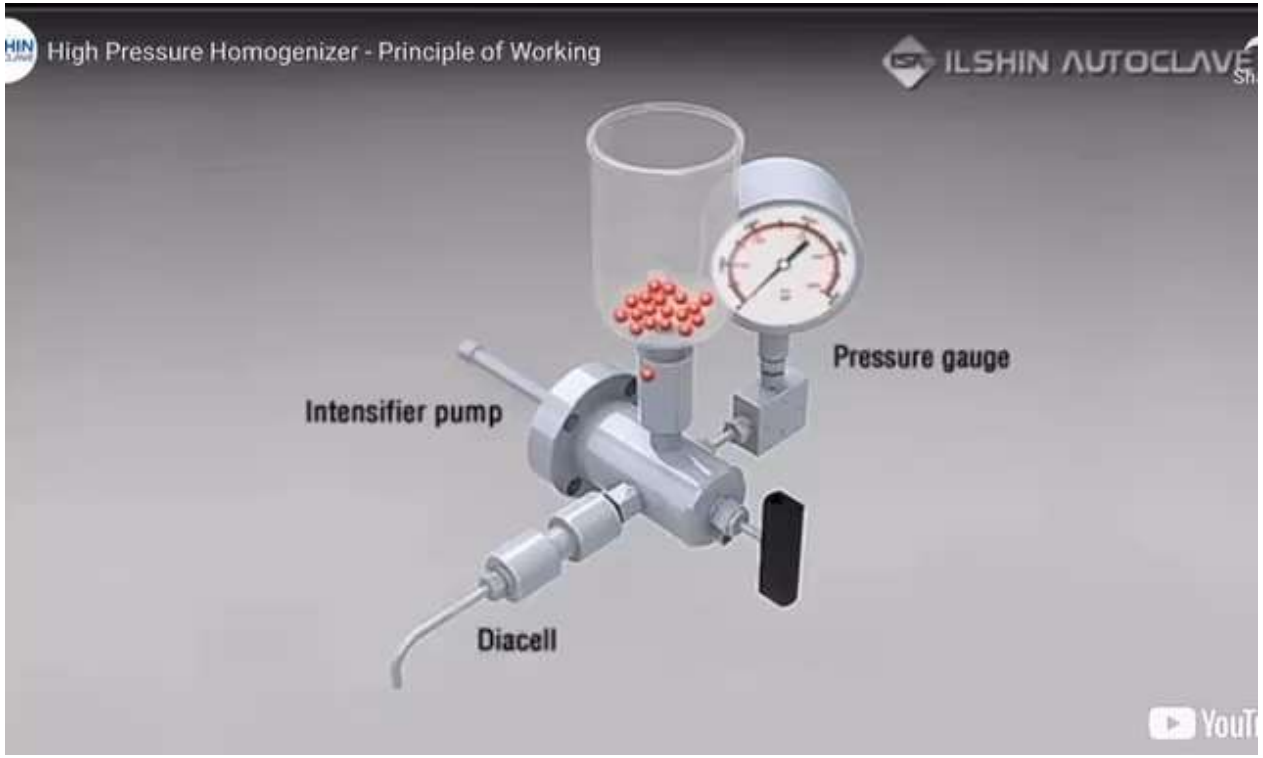
Different from other Nano preparations such as liposomes, nanoparticles, and other solid lipid nanoparticles as drug nanocrystals have a simple composition, usually contain only pure drugs, and may include small amounts of stabilizers thereby minimizing accessory related toxicity.

the high drug loadings of drug nanocrystals is increased patient compliance.

Methods for preparation classified as:

1-Top-down technology which include :

A-high-energy process called high-pressure homogenization:



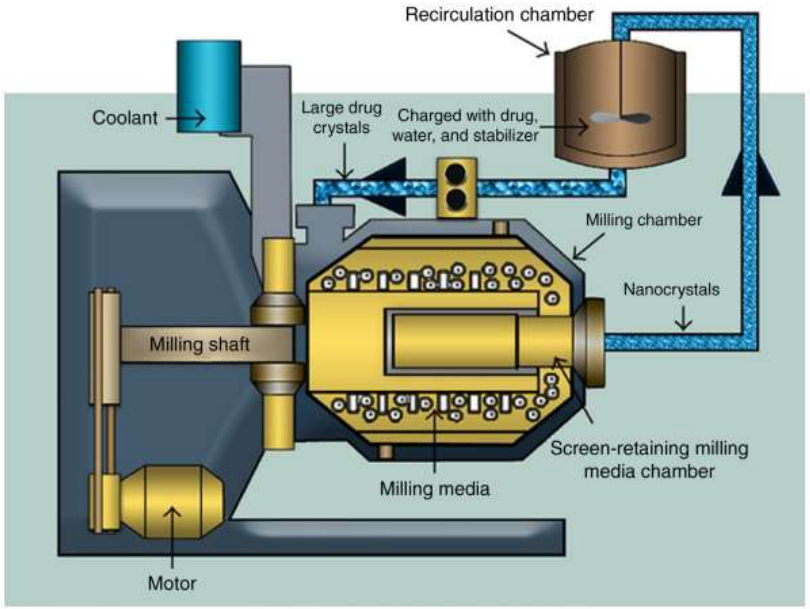
B- Low-energy process called (media milling) :

The aqueous suspension of the drug and stabilizers filled in the milling chamber and the milling media or pearls rotate at a very high shear rate, thus forming drug nanoparticles from friction and collisions.

Advantages: of media milling are subtle batch-to-batch variation and facile scale-up.

Disadvantage: this method may cause the erosion of pearls that might contaminate drug nanoparticle Product.

Shearing can generate a lot of heat, and this procedure can be undertaken with controlled temperature.



bottom-up (antisolvent precipitation):

The commonly utilized bottom-up techniques are:

1- antisolvent precipitation: generally, the drug is first dissolved in a solvent, to which the antisolvent is then added in the presence of a surfactant. The rapid formation of the drug precipitate results in the sudden supersaturating of drug in the mixed solution, thus forming the ultrafine crystalline or amorphous drug nanoparticles.

2- precipitation-ultrasonication:It was found that the crystal size can be reduced by simply increasing the applied ultrasonic power due to the fact that ultrasound irradiation can promote the molecular diffusion and mass transfer, 400 W power input is enough to achieve the optimal particle size reduction. In addition, the time that the drug particle is exposed to ultrasonication has an effect on the nanoparticle size. It was found that the particle size is significantly decreased if the ultrasonication time was extended to 15 min.

Limitations:

The instability of nanocrystals has been hindering their development and production.

The instability of nanocrystal preparations is primarily due to the small particle size that cause high surface energy so the particle size will increase to reduce the surface energy during storage leads to thermodynamic instability, which eventually leads to aggregation, Ostwald ripening and sedimentation.

aggregation

aggregation between crystals is one of the main reasons for its low stability. Particles in suspension exhibit Brownian motion, and they can collide, stick together, and coalesce due to the attraction between the particles and van der Waals forces.

The aggregation of nanoparticles increases the particle size, broadens the particle size distribution, and, thus, reduces the solubility and dissolution rate of drugs.

Aggregation

Ostwald ripening (crystal growth) :

A phenomenon in which crystals of various particle sizes grow due to differences in solubility.

Since small crystals have higher surface free energy, they have higher saturation solubility than large crystals, which leads to a drug concentration gradient between crystals. A smaller crystal interacts with a larger crystal, and the resulting diffused mass exchange causes the larger crystal to grow further and the smaller crystal to shrink and disappear

Ostwald Ripening

3-sedimentation

Sedimentation is a common cause of instability of nanosuspension, particles of larger size settle naturally under the action of gravity.

The sedimentation behavior of Nanocrystals can be divided into two types:

Flocculation and deflocculation.

Flocculating suspensions are characterized by rapid and loose sedimentation, and sediments are easily redispersed.

deflocculation suspensions show a slow and dense settlement and sediments are difficult redispersed.

Sedimentation

factors affecting nanocrystals preparation:

Drug-related factors

The formation of nanocrystal suspensions is influenced by the physical and chemical properties of the drugs, including

A- Drug polymorphism

Many factors influence the molecular arrangement in drug nanocrystals, such as the solvent, temperature, and preparation process. The polymorphic forms and physical stability and solubility vary among arrangements.

Therefore, in the formation of stable drug nanostructures, the polymorphic forms of drug nanocrystals must be considered. Compared with crystalline forms, amorphous forms are relatively unstable, and amorphous drugs are more soluble and prone to Ostwald ripening.

B-Drug hydrophobicity(log P):

George & Ghosh (2013) found that drugs with high Log P values form highly stable nanosuspensions.

The researchers believe that the attraction between the hydrophobic surface of the drug and the hydrophobic functional group of the stabilizer leads to the strong adsorption of the stabilizer on the drug surface and that hydrophobic drugs are more suitable than hydrophilic drugs for nanocrystal preparations because of the risk of reversible dissolution and precipitation.

C-Drug enthalpy :

Enthalpy represents the strength of the intermolecular interactions.

George & Ghosh (2013) found that drugs with low enthalpy are prone to aggregation during the storage process due to the low enthalpy of these compounds, the crystal structures of drugs in water are easily destroyed, which may lead to a transition from a crystalline form to an amorphous form, thereby leading to the instability of the drug nanosystem.

2. Stabilizing agent related factors:

A- type of stabilizer:

The surface tension of drug nanocrystals is often very high, which leads to the facile aggregation of drug particles. The use of a suitable stabilizer can reduce the surface tension and prevent the aggregation of nanocrystals.

Ionic surfactants stabilize suspensions by initiating electrostatic repulsion between drug nanocrystals.

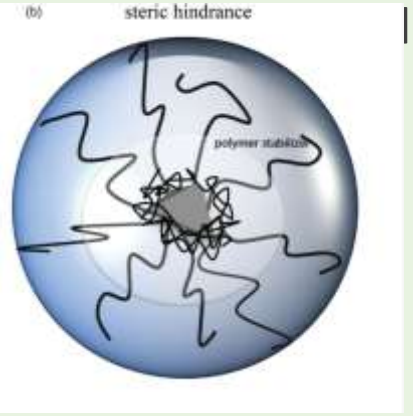
Polymers and nonionic surfactants maintain the stability of suspensi l barriers.

The long hydrophilic chains of the polymers that are adsorbed

on the nanocrystal surface extend further outward, thereby

limiting the movement of drug particles to maintain

the distance between drug particles



- The stability of nanosuspension system stabilized by electrostatic repulsion can be inhibited and may be destroyed by the electrolytes or high acid conditions.

  The stability of the nanosuspension system stabilized by steric hindrance is not disturbed by charge ions, but the interaction between the stabilizer and the drug is more complex, the suitable polymer should be selected according to the physical and chemical properties of the drug.

- Suspensions containing high concentration polymers and drugs are often not conducive to the preparation of nanosuspensions because of their high viscosity.

B-Molecular weight of the stabilizer:

The hydrophobic end of the polymer stabilizer adsorbs on the surface of the drug nanocrystal, which can provide spatial stability, and stabilizers with higher molecular weight typically outperform stabilizers with lower molecular weight.

A long-chain polymer stabilizer can effectively induce spatial repulsion and prevent the aggregation of particles.

A polymer stabilizer with a molecular weight of less than 5000 g/mol has difficult forming a spatial barrier for the mutual attraction between particles.

a polymer stabilizer with a molecular weight that exceeds 25,000 g/mol may lead to nanocrystal bridging due to the large molecular chain length.

C- hydrophilic and hydrophobic properties of the stabilizer(HLB):

To improve the stability of drug nanocrystals, the stabilizer should have sufficient affinity with the surfaces of the drug particles.

When insoluble drugs show high hydrophobicity, the hydrophobicity of the stabilizer is the main driving force for the surface adsorption of the drug particles, which is crucial for the spatial stability and uniform dispersion of the drug particles.

Moreover, the hydrophilicity of the stabilizer is important because most drug nanocrystals are dispersed in water and the hydrophilic portion of the stabilizer will be oriented toward water rather than the hydrophobic surface of the drug, thereby facilitating the inhibition of the drug nanocrystal aggregation.

D- concentration of the stabilizer:

The stability of a nanosuspension is not directly proportional to the concentration of the stabilizer.

The optimal stabilizer concentration will maximize the adsorption affinity of the stabilizer to the drug surface.

Spatial repulsion is induced by coating drug nanocrystals with stabilizers to prevent Ostwald ripening, therefore, if the stabilizer concentration is insufficient, the drug particles cannot be effectively coated.

If the drug particles are attached to the same stabilizer molecule, particle aggregation and bridging can occur, thereby resulting in reduced stability.

Excessive stabilizer may lead to Ostwald ripening and decrease the stability over time.

In addition, amphiphilic stabilizers in concentrations that exceed the critical micelle concentration (CMC) may lead to micelle formation.

3- combined action factor

A- Drug solubility in a stabilizer solution:

The solubility of a drug is affected by the type of stabilizer that is used. When the solution of stabilizers increases the solubility of drug nanocrystals, the stability of these crystals decreases over time, thereby leading to the growth of the nanocrystals.

Therefore, the stabilizers with the weakest influence on the drug solubility are the first choices for the preparation of a nanosuspension.

Effects of dispersion media:

To form a stable nanosystem, the temperature and viscosity of the dispersion medium must be suitable. The Stokes–Einstein equation can be used to explain the influence of the temperature and viscosity on the stability of the nanosuspension

According to the Stokes–Einstein equation, high viscosity $D = kT/(6\eta\pi r)$ particles and, thus, stabilizes the nanosuspension.

The higher the temperature of the nanocrystal system, the lower the stability of the system.

However, an increase in the temperature will lead to a decrease in the viscosity and an increase in the diffusion coefficient, which is very unfavorable for the inter actions between particles in the nanosystem.

Thank you..