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FORMULATION AND EVALUATION OF ORAL TABLET DOSAGE FORM INCORPORATING NANOSUSPENSION OF ANTIRETROVIRAL DRUG: A REVIEW

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ABSTRACT

Antiretroviral drugs used in HIV treatment often suffer from poor aqueous solubility and low oral bioavailability, resulting in reduced therapeutic effectiveness. Nanosuspension technology has emerged as an effective strategy to improve dissolution rate, absorption and bioavailability of poorly soluble drugs. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilised by surfactants or polymers. Incorporation of nanosuspensions into oral tablet dosage forms combines the benefits of nanotechnology with the convenience and stability of tablets. This review summarises various methods of nanosuspension preparation, formulation approaches, characterisation techniques and evaluation parameters of nanosuspension-based oral tablets containing antiretroviral drugs. The review also highlights recent advancements, advantages, limitations and future perspectives of nanosuspension technology in HIV therapy.

KEYWORDS

Nanosuspension, Antiretroviral drugs, Oral tablets, Bioavailability and Nanotechnology.

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INTRODUCTION

An increasing number of medications, whether in development or already available for purchase, fall into the low aqueous solubility category. Low solubility is one of the most common causes of poor oral bioavailability. Low water solubility limits oral bioavailability, while fixed-dose combinations necessitate enhanced personalization. Consequently, fluid bed granulation of drug nanosuspensions to produce minitablets with customized dissolution profiles enables tailored release characteristics by

utilizing the nanosuspension as a binding agent. An API nanosuspension was mixed with polymeric excipients, specifically HPMC grade E5 and PVP K 30. Fluid bed granulation was performed using a MINI-Glatt system with a top-spray configuration on either pearlitol or Avicel. Combining minitablets with "fast" and "slow" release profiles in ratios of 3:7, 5:5 and 7:3 yielded consistent dissolution curves. This approach enables a reliable, adaptable, and logical design for precision medicine that is rooted in patient physiology. It allows for the precise customization of drug release profiles to align with individual gastrointestinal transit times. For instance, cardiovascular diseases often require combination therapy with multiple medications and research shows that fixed-dose combinations (FDC) significantly improve treatment outcomes.

Ocular delivery will also encounter challenges with drugs that exhibit low solubility. Managing chronic conditions demands sustained long-term compliance. To address this, long-acting injectables enhance compliance, yet developing a stable formulation remains challenging. Long-acting injectables (LAIs) prepared via the dual centrifugation (DC) method using nano microsuspensions. Suspensions were prepared using stabilizers (P188, SDS, PS20) at various critical micelle concentrations. A DeltaVita 1 dual centrifuge was run at 1500rpm for 90 minutes using different zirconia bead sizes. DC enhances a standard centrifuge by adding an extra rotary plate, which increases contact points and improves efficiency. This method is ideal for small-scale screening, capable of processing up to 40 small vials at once. Dual centrifugation offers a rapid, reproducible, small-scale screening approach for long-acting injectable formulations.

To enhance the dissolution rate and physical stability of the NSAID ketoprofen, nanosuspension was identified as the suitable approach. As a BCS class II drug, ketoprofen exhibits high permeability but low solubility, resulting in reduced plasma absorption. Fluctuations, stomach infection, or bleeding. Polyvinyl pyrrolidone (PVP) and Tween 80 were employed as stabilizers in varying ratios with the drug. The nanosuspensions achieved stable particle sizes in the nanoscale range of 78nm. Forty-seven nanometers (at a 1:1 ratio) and 156. A ratio of 1:1. 5 at nine nanometers. The formulations demonstrated remarkable physical stability in pH, color, and particle size at room temperature over a period of three months. Substantially greater than those of standard stops. The combination of PVP and Tween 80 optimized ketoprofen dissolution while successfully maintaining long-term physical stability. Celecoxib is a BCS class II drug characterized by low aqueous solubility, resulting in poor and incomplete oral bioavailability. Prepare celecoxib (CLX) nanoparticles using antisolvent precipitation combined with high-pressure homogenization. Soluplus demonstrates a promising solubility-enhancing effect on crystallized celecoxib produced via antisolvent precipitation. Soluplus (SOL) is a graft copolymer with amphiphilic properties that has been modified to serve as a unique hydrophilic stabilizer. The antisolvent crystallization followed by freeze-drying (CRS-FD) process was modified in comparison to the high-pressure homogenization followed by freeze-drying (HPH-FD) method. The samples underwent comprehensive evaluation using DSC, XRPD, FT-IR, SEM and saturation solution analysis. DSC and XRPD analyses revealed that samples processed via the HPH method exhibited enhanced crystallinity. CLX nanoparticles with higher crystallinity demonstrated superior dissolution behavior compared to their amorphous counterparts.

Human immunodeficiency virus (HIV) continues to be a significant global health challenge. While antiretroviral therapy has greatly enhanced patient survival, many antiretroviral tablets suffer from poor solubility and inconsistent bioavailability. Conventional oral dosage forms often fail to provide adequate drug absorption. Nanosuspension preparation is a widely adopted method to address these limitations by reducing drug particle size to the nanometer scale, which enhances both surface area and dissolution rate. Integrating nanosuspensions into tablets enhances stability, patient compliance, and curative efficacy.

NANOSPENSIONS TECHNOLOGY

Nanosuspensions are submicron colloidal dispersions of pure drug particles stabilized by surfactants.

Advantages

Enhanced bioavailability is achieved by increasing dissolution pressure through reduced particle length, which facilitates faster absorption and improved therapeutic efficacy.

High drug loading allows formulations to contain up to 100% pure live pharmaceutical ingredients with minimal excipient interference.

Reduced food exposure minimizes fluctuations in drug plasma levels between fasted and fed states.

Reduced inter-subject variability ensures highly reproducible drug absorption rates across different patients.

It offers versatile routes of administration, including oral, intravenous, ophthalmic, topical, pulmonary, and subcutaneous formulations.

Safe intravenous delivery is ensured because submicron particle sizes prevent blockage of blood capillaries during injection.

The ease of large-scale production allows for straightforward implementation of top-down processes like excessive flow homogenization in industrial settings.

Reduced toxicity: Minimizes adverse effects caused by chemical solvents or excessive amounts of toxic excipients.

Limitations

Physical instability arises because nano-sized debris exerts excessive floor force, thereby heightening the risk of aggregation, sedimentation, and compaction over time.

Ostwald ripening occurs when small crystals dissolve and redeposit onto larger ones, leading to a non-uniform particle distribution.

The top-down milling technique poses a contamination risk due to the erosion of milling media, which significantly increases the likelihood of product contamination.

Dosage inaccuracy can occur if the suspension is mishandled, improperly delivered, or incorrectly prepared, leading to uneven dosing.

Microbial growth potential: Extended wet-milling processes in aqueous environments carry a risk of microbial proliferation during production.

Thermolabile limitations: High temperatures occurring at various stages of the manufacturing process can damage heat-sensitive drug additives.

Antiretrviral drugs, used in nanosuspensions

Although antiretroviral tablets are essential for long-term treatment, their poor aqueous solubility often necessitates excessive and frequent dosing, which can lead to reduced patient compliance. Oral drug delivery remains the preferred method of administration due to its comfort and patient compliance. However, a significant hurdle in developing oral formulations is the poor aqueous solubility of many drugs, particularly antiretrovirals. Most antiretroviral drugs belong to BCS class II, characterized by low solubility and high permeability, which leads to poor dissolution rates and inconsistent oral bioavailability. Nanosuspension technology enhances drug solubility and dissolution by reducing particle size to the nanometer range. While liquid nanosuspensions offer significant advantages, they frequently face challenges related to stability and storage.

Several antiretroviral drugs, which are poorly soluble, are well-suited for nanosuspension formulation, including:

Darunavir
Efavirenz
Ritonavir
Atazanavir
Dolutegravir

METHODS OF PREPARATION

Primarily, there are two methods for preparing nanosuspensions.

Top-down approach to technology

Top-down technology" refers to fragmentation techniques that are favored over precipitation methods. The 'Top-Down technology' encompasses media milling for nanocrystals, high-pressure homogenization in water using Dissocubes, high-pressure homogenization in non-aqueous solvents

with Nanopure and a combined approach of precipitation and high-pressure homogenization via Nanoedge.

Media Milling (Nanocrystal or Nanosystems)

The method was primarily developed and documented based on the work of Liversidge et al. (1992). Nanosuspensions are prepared using high-shear media generators. The milling chamber, containing the milling agent, water, drug, and stabilizer, is rotated at extremely high shear rates while temperature is carefully controlled. The milling medium consists of glass, zirconium oxide, or polystyrene resin with extensive pass-related properties. The collision between the milling agent and the drug generates high electric shear forces, resulting in the reduction of microparticles. tablets to nanoparticles. Media milling is an appropriate technique for capsules that exhibit low solubility in both aqueous and organic solvents. Nanosuspensions that are either highly dilute or sharply focused can be produced by this method. Administer drug concentrations ranging from 1mg/ml to 400mg/ml. The final product can be manufactured through nanoscale diffusion. Drawback The primary risks associated with this technique are the erosion of spheres or beads, which can lead to residual contamination of the final product, and the degradation of thermolabile tablets due to heat generated within the system.

Advantages

Media milling is good for making capsules that don't dissolve easily in water or other liquids.

It can make nanosuspensions that are either very thin or very concentrated, by using drug amounts from 1mg/ml up to 400mg/ml.

The final product can be made through nanoscale diffusion.

Drawback

The main problems with this method are that the small beads can break apart, leading to leftover dirt in the final product and heat can damage heat-sensitive tablets.

High Pressure Homogenization:

This process has three steps.

First, the drug is mixed with a stabilizing agent to make a pre-suspension. Then this mixture goes through a homogenizer with low flow to begin breaking down the particles. This is done using overflow homogenization for 10 to 25 cycles, which creates the final nanosuspension. Different methods like dissocubes, nanoreins and nanodomains are based on this idea.

Homogenization in aqueous medium (Dissocubes)

This method was first introduced by R.H.

Muller using a high-speed homogenizer with a piston-hole design. The drug and surfactant are forced through a narrow opening in a high-pressure homogenizer. The idea is based on cavitation, where water starts boiling at room temperature due to the sudden pressure drop when the flow goes through a small gap. This creates bubbles that burst as the mixture exits, which helps break the drug into smaller particles.

Advantages:

This method doesn’t use the operating system.

It works well for drugs that don’t dissolve in water or natural solvents.

Disadvantages:

The drug needs to be broken into smaller particles before processing.

It’s expensive because special equipment is required.

Homogeneity in non-aqueous medium (Nanopure)

Nanopure is a suspension made in non-water-based media or mixtures like PEG 400 or PEG 1000.It can be made at room temperature, 30°C, or even at very low temperatures like -200°C, which is why it's also called homogeneous freezing.

Nanoedge Generation

This method combines precipitation and homogenization.

The main idea is the same as both of these methods. It helps fix problems like slow crystal growth and long-term balance that happen with precipitation. This method makes smaller, more uniform articles quickly.

Nanojet Time

Nanojet, also known as counter-flow technology, uses a chamber where the suspension is split into smaller parts, which then collide under high pressure.

The strong shear forces from this process reduce the size of the particles.

Dry Grinding

Dry co-grinding is a method where hard-to-dissolve tablets are ground together with soluble polymers or copolymers.

This has been successfully used to make nanosuspensions by grinding insoluble drugs with soluble polymers and copolymers in water.

Advantages

A simple and reasonable way to make particles.

No use of natural solvents.

Makes solid, amorphous particles smaller than a micron.

Bottom-up technology

Traditional methods of making medicines, called 'Bottom-up production,' involve dissolving the drug in a solvent and then mixing it with a non-solvent to form crystals.

This method was used by Sucker and others to make nanoparticles by dissolving the drug in a solvent and then mixing it with a non-solvent, which causes the drug to form small particles. One main advantage of this technique is that it uses simple and affordable equipment. However, a problem with this approach is that when making the crystals, you need to carefully control their size by adding a surfactant to stop them from forming large debris. A disadvantage is that the drug must be able to dissolve in a solvent that can also mix with the non-solvent.

Lipid Emulsion and Microemulsion Techniques

Lipid emulsions can be used to make medicines that dissolve in partially mixed solvents or natural solvents that evaporate easily.

This method involves mixing the drug with a surfactant to form an emulsion. When the natural component evaporates, the drug particles settle down and form a nanosuspension that is stabilized by the surfactant. This method is used for medicines that can dissolve in natural solvents or have some water solubility. The drug is mixed with an organic liquid and then with water. Removing the solvent under pressure causes the drug to quickly form nanocrystals and nano-sized suspensions.

Advantages

You can control the size of the particles by controlling the size of the emulsion droplets.

Once the formula is set right, it's easy to scale up the process.

Disadvantages

This method doesn't work for medicines that can't dissolve in water or organic solvents.

Purifying the product needs ultrafiltration, which makes the process expensive.

A lot of surfactants are required.

Melt Emulsification Method

This method involves mixing the drug with an aqueous stabilizer and then heating it above the melting point of the drug to create an emulsion through homogenization and cooling.

This process helps form nanoparticles. One benefit of this method is that it doesn't use organic solvents.

Liquid Antisolvent Precipitation

This is the most commonly used bottom-up method and is simple, low-cost, and uses no solvents.

It involves mixing a drug solution with an antisolvent to create a supersaturated solution that quickly forms small particles. Uniform mixing ensures that the process is controlled and results in very small and evenly sized particles. However, the solvent must be quickly removed from the final suspension.

These methods help make the particles smaller and improve how well the medicine dissolves.

Used Excipients

Conventional Stabiliser

A stabiliser is very important in making nanosuspensions.

It stops the nanoparticles from sticking together and forming larger debris. It helps in keeping the drug particles stable and prevents them from clumping, which can happen quickly without it. The stabiliser creates a physical or electrical barrier around the nanoparticles.

Features

Prevents Clumping: It forms a physical or electrical barrier between the nanoparticles.

Stops Ostwald Ripening: It prevents smaller particles from dissolving.

Helps Wetting: It reduces the surface tension between the drug and water, making it easier for the drug to spread evenly.

Some of the common stabilizers include:

Hydroxypropyl methylcellulose (HPMC)

Poloxamer

Polyvinyl pyrrolidone

Tween 80

Polysorbate

Povidone

Lecithin

Eudragit

Cosurfactants

Using co-surfactants greatly affects how microemulsions work, how neatly tablets are trapped, and how the machine behaves.

Examples of cosurfactants include bile salts, dipotassium glycyrrhizinate, ethanol and isopropanol.

Organic solvents

Choosing the right organic solvent is critical to safety and efficacy.

The solvent should be safe to use in repair and no longer too risky. Examples include ethanol, methanol, isopropanol, ethyl acetate, butyl lactate and propylene carbonate.

Osmotic compounds

Osmotic vendors are key components in nanosuspension formulation.

They help shop the balance of salt within the response, manipulate how the drug is launched, and maintain the stability of the framework. These targets create a flow difference that continues the response that matches the body's cells, stopping tissue damage. affect how nanoparticles behave in water, contribute to preventing them from clumping together or changing length over the years.

Examples: Sodium chloride, sucrose, potassium chloride.

Cryoprotectants

Cryoprotectants are critical compounds delivered to nanosuspensions prior to freeze-drying.

They protect nanoparticles from clumping or developing too giant by preventing ice crystals from destroying them during freezing. Without them, nanoparticles can stick together or fuse, which can lose their small length and rapid dissolution ability.

Example: Trehalose, sucrose.

Other excipients

Buffers

In pharmaceutical nanosuspension, a buffer is a vital component used to keep the pH level constant.

Because nanoparticles have a massive surface area, they are highly touchable to changes in their environment. These adjustments can have an impact on the structure and stability of the drug.

CONVERSION INTO TABLETS

Liquid nanosuspensions are usually transformed into stable dose bureaucracies to improve physical equilibrium, ease of handling, transportation, and affected person compliance. However, the chosen conversion method aims to preserve the nanoparticle size and allow green redispersion upon administration.

Spray drying

Spray drying is one of the most widely used strategies to convert nanosuspensions into dry powders. In this machine, the nanosuspension is atomized into sufficient droplets and exposed to a movement of hot air, manifested by rapid solvent evaporation and formation of dry debris. The method is fast, scalable, and suitable for mass production. Spray-dried powders can be simultaneously pressed into tablets or additionally processed into granules. Proper selection of drying conditions and excipients is essential to prevent particle aggregation and to preserve nanoparticle homes.

Freeze drying/Freeze drying

Lyophilization is a dehydration system in which the nanosuspension is first frozen together via sublimation under reduced stress. Water is immediately removed from the frozen nation,

resulting in a porous dry cake containing dispersed nanoparticles. This method reduces heat stress and is particularly suitable for heat-touching drugs. Cryoprotectants composed of mannitol, trehalose, or sucrose are regularly delivered to protect nanoparticles at some stage of freezing and desiccation. The subsequent product known high-quality stability and can be resultaseasyly reconstituted earlier than administration or formulated into capsules.

Fluid bed granulation

Wet-bed granulation is a complex method in which nanosuspensions are sprayed onto liquid auxiliary debris to form granules. The nanosuspension acts as a binder and simultaneously deposits drug nanoparticles on the substrate. This technique improves the powder plate housing, content uniformity, and compressibility. Granules obtained using fluid bed granules can be compressed into tablets even as retaining nanoparticle redispersion and higher dissolution properties. The method is extremely suitable for the economic production of nanosuspension-based totally completely oral dosage forms.

Direct compression

Direct compression involves mixing dried nanosuspension powders with appropriate excipients by applying stress to tablets with no intergranulation step. It is an easy, cost-effective and time-saving production tool. The technique requires powders with proper flowability and compressibility to ensure uniform tablet production. Appropriate thinners, binders, decomposers, and lubricants are necessary to harvest favorable tablets home. Direct compression reduces treatment rates and reduces the possibility of nanoparticle growth, thus preserving the dissolution benefit of nanosuspensions.

Successful conversion of nanosuspensions into drugs relies on maintaining nanoparticle duration, preventing aggregation and ensuring rapid redispersion after administration. Appropriate system setup and operating conditions are thus crucial to maintain the advanced resolution and bioavailability provided by means of the nanosuspension feeding.

EVALUATION OF THE NANOSUSPENSION

Comprehensive characterization of nanosuspensions is critical to ensure their flavor, balance, and overall performance. Various physicochemical parameters are evaluated to determine the suitability of nanosuspensions for oral drug delivery packages.

Analysis of particle size

Particle size is one of the most important parameters that affect solution charge, saturation solubility and bioavailability. Dynamic light scattering (DLS) is commonly used to determine collective particle length and length distribution of nanosuspensions. Smaller particle sizes provide a larger surface area, which leads to better dissolution and absorption.

Polydispersity Index (PDI)

The polydispersity index suggests that the particle length distribution is uniform. A polydispersity index value below zero, usually indicates a homogeneous nanosuspension with a slim particle length distribution. Lower PDI values contribute to superior compatibility and reproducibility.

Zeta potential

Zeta potential is a measure of the surface charge of nanoparticles and is used to anticipate physical equilibrium. High prominent or low zeta potential values create electrostatic repulsion between particles, thereby stopping the aggregation. Preferably, zeta potential values of more than ±30 mV achieve accurate equilibrium.

Drug content

Analysis of drug containing material ensures even distribution of the potential pharmaceutical substance sooner or later within the process. Accurate drug loading.

Saturation resolution

Particle length discounting will boom saturation solubility in accordance with the Ostwald-Freundlich equation. Determination of saturation solubility offers facts regarding the amount of solubility enhancement achieved through nanosizing.

***In Vitro* Dissolution Studies**

Dissolution experiments were performed to evaluate the drug release behavior of nanosuspensions. Increased dissolution cost is generally observed due to extended surface affinity and advanced wettability of nanoparticles.

Crystalline State Analysis

X-ray powder diffraction (XRPD/XRD)

XRPD is used to determine which drug particles are crystalline or amorphous. Changes in crystallinity can also affect drug dissolution and stability.

Differential scanning calorimetry (DSC)

DSC is used to study thermal conductivity, melting point, and potential drug-excipient interactions.

Fourier transform infrared spectroscopy (FTIR)

FTIR assessment identifies concrete systems and evaluates drug-excipient compatibility.

Morphological studies

Scanning electron microscopy (SEM)

SEM provides targeted data regarding particle morphology, floor morphology, and aggregation behavior.

Transmission electron microscopy (TEM)

TEM offers excessively high-resolution images of nanoparticles and allows direct visualization of particle size and morphology.

Stability studies

Physical equilibrium studies have been conducted under unusual garage conditions to evaluate changes in particle rate, zeta capacity, drug containing cloth, and dissolution performance over the years.

EVALUATION OF TABLET

After conversion of nanosuspensions to capsules, complete evaluation is necessary to ensure proper pharmaceutical quality and performance.

Weight Variation

Weight variance testing confirms dose equivalence between drugs. Individual tablet weights are when it comes to pharmacopoeial specifications.

Thickness

Tablet thickness is measured using a vernier caliper or a digital thickness meter. Uniform thickness is vital for packaging and affected grade certification.

Hardness

Hardness determines the mechanical strength of capsules and their ability to resist crushing, transportation, and garaging.

Fragility

Friability checking out evaluates the tendency of capsules to disintegrate or shatter during the handling path. A friability rate below 1% is usually accepted as it should be.

Drug content uniformity

Uniform drug content material ensures that each tablet carries the purported amount of energetic pharmaceutical element.

Disintegration time

Disintegration look at determines the time required for drugs to fall apart into smaller debris in an aqueous environment.

Dissolution research

Dissolution experiments have been performed to study drug release profiles between nanosuspension-loaded drugs and standard formulations. Increased solution conductivity is regularly located due to the presence of nanocrystalline drug particles.

Stability Research

Tablet pharmaceutical studies studies investigate the results of environmental conditions by lateral temperature and humidity of product fines, drug-containing materials, dissolution habitats, and physical appearance.

Recent Advances in Nanosuspension-Based Oral Drug Delivery

Recent features in nanosuspension practice have expanded their packages in oral drug delivery structures.

Surface modified nanosuspensions

Surface modification using polymers and surfactants improves nanoparticle stability, enhances mucosal adhesion, and prolongs residence time in the gastrointestinal tract.

Mucoadhesive nanosuspensions

Mucus adhesive polymers had been integrated into nanosuspensions to enhance intestinal retention and absorption of boom medicine.

Grain size in liquid bed

Advanced liquid-mattress granule technology has enabled the transformation of nanosuspensions into granules and minitablets while maintaining nanoparticle housings and improving dissolution medium performance.

Personalized oral dosage forms

The integration of nanosuspension preparation with minitablet and multi-unit dosage form systems has provided opportunities for personalized therapy through tailored drug release profiles.

Long-acting oral formulations

Research efforts are focused on increasing the sustained release and controlled release of nanosuspension-based general-dose formulations that improve patient compliance and healing outcomes.

Targeted drug delivery structures

Nanotechnology-primarily based overall tactics are increasingly explored for web site-specific shipping, desirable mobile uptake and advanced healing efficacy.

Future Perspectives

The direction of nanosuspension preparation is extremely promising for the development of oral formulations of poorly water-soluble antiretroviral tablets. Advances in nanotechnology, fabrication processes, stabilizer selection, and casting techniques are expected to facilitate the commercialization of products primarily based on nanosuspension. Integration with personalized therapies, controlled release systems, and targeted drug delivery technologies may also further enhance the curative efficacy, even as improving the compliance of the affected individuals.

Further studies are needed to overcome challenges related to long-term stability, large-scale production, regulatory approval and cost-effectiveness.

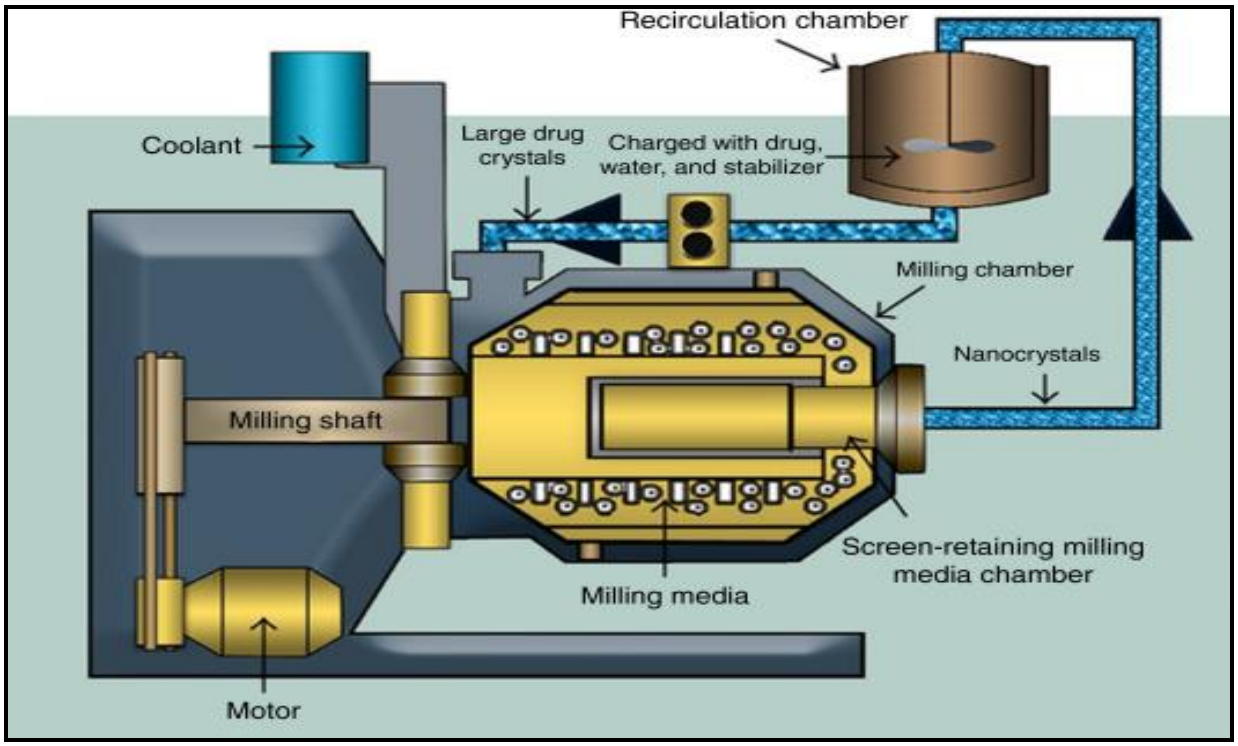


Figure No.1: A diagram showing the Nano milling process

CONCLUSION

Nanosuspension preparation represents an extremely powerful method to overcome the solubility and bioavailability barriers associated with many antiretroviral drugs. By reducing the drug particle rate to the nanometer range, nanosuspensions significantly enhance the solute loading, saturation solubility and gastrointestinal absorption. Various techniques, along with media milling, over-speed homogenization, nanoprecipitation and solvent evaporation, had been used to achieve accurately sized overall performance in producing solid nanosuspensions.

The incorporation of nanosuspensions into oral tablet dosage form formulations through spray drying, freeze-drying, fluid-mattress granulation and direct pressure provides massive benefits in terms of balance, comfort and patient compliance. Comprehensive characterization and evaluation ensure product fineness and overall performance. Recent advances in personalized therapeutics, targeted shipping, and given-release formulations similarly highlight the potential of nanosuspension-based entirely oral drug delivery systems. Thus, nanosuspension-loaded drugs are a promising platform to beautify the curative effect of antiretroviral therapy and other poorly water-soluble tablets.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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