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ABSTRACT
Nanotechnology includes nanosuspensions. The term "nanosuspensions" refers to submicron colloidal dispersions of pharmaceutical active ingredient particles in a liquid phase with a size of less than 1 µm and no matrix material. These dispersions are stabilized by polymers and surfactants. Nanosuspensions are distinct from both solid lipid and polymeric nanoparticles in that the former are lipid carriers of medications while the latter are polymeric colloidal carriers of drugs. All medications that are water insoluble can benefit from the easy preparation of nanosuspensions. Emulsion solvent evaporation, melt emulsification, high pressure homogenizer, wet mill and supercritical fluid processes are used to prepare nanosuspensions. Oral, parenteral, pulmonary and ophthalmic administration are available for nanosuspensions. Combined with ocular delivery systems nanosuspensions can also be utilized for targeted drug delivery.
Keywords: Nanotechnology, Nanosuspension, Bioavailability, Solubility.

INTRODUCTION

A more recent advancement in suspension is nanosuspension. For the medication formulation its effectiveness depends on a number of factors such as the stability at room temperature, including as solubility, compatibility with excipients and solvents and photostability. Currently, about 40% of newly identified chemical entities in the process of medication development are lipophilic or soluble poorly in water, substances. These methods, however, often fall short of expectations when it comes to making poorly soluble medications more soluble. Though they are not always suitable for all medications, other approaches including vesicular systems like liposomes, solid dispersions, emulsions, microemulsions and inclusion complexes containing cyclodextrins have shown potential as drug delivery methods. Nanoparticle engineering has been a major advancement for medicinal applications in the last several decades

Poorly water-soluble medicines rate of dissolution sometimes restricts their GI tract absorption. Many solubilisation approaches are used including the application of dispersion, polymeric bonds, surfactant and soluble in water carriers to enhance the solubility and dissolving capabilities of medications. Pharmaceutical nanosuspensions have shown to be a simpler and more affordable technical alternative to liposome dispersions particularly for medicines that are insoluble. Physically the finished product is more stable. Using shear pressures

after dissolving it into water it is broken up into small pieces.[4] Due to their greater dissolving pressure brought on by their

smaller size the dispersed particles dissolve more quickly increasing their saturation solubility. When compare to different methods this may improve the BA of medications. If the drug particles dissolve slowly enough *in vivo* drug nanosuspensions will benefit from colloidal drug carriers passive targeting capabilities.[5]

The Noyes Whitney equation provides us with a number of ways to enhance the restricted dissolution that are weakly miscible in water. The primary strategy here is to enhance the dimension of the particles by using milling to reduce their size. Aggregation on the other hand might result from this increasing particle size and eliminating the original benefit. As a control in this case an ITZ nanosuspension was made Reducing the particle size for the experiment and therefore the inherent diffusion layer thickness is another technique occupied to lessen the thickness of the boundary layer. It is also essential to enhance the compound's perceived solubility is also essential. Due to the inadequate solubility of ITZ many techniques have been used to increase its perceived solubility which in turn improves dissolution and eventually oral absorption.[6]

When particles bigger than 1000 nm are evenly dispersed and visible to the unaided eye in a combination it is referred to be a suspension. All of the ingredients are combined in this combination and a microscope can clearly see the particles. The solid particles in a suspension in contrast to solutions remain suspended in the solvent and are big enough to scatter light making the light path visible through the combination. A heterogeneous mixture that includes solid particles usually bigger than one micrometre that are big enough to settle over time is referred to as a suspension in chemistry. As long as the particles are in suspension and do not totally settle out the combination is regarded as being in suspension.[7]

With a plethora of uses nanotechnology and associated technologies have greatly increased formulation development productivity. Early in the drug development phase conventional formulation techniques are often abandoned because of the materials poor water solubility. The solubility of a pharmaceutical is crucial for its efficacy regardless of the manner of administration. Formulations based on nanotechnology have successfully tackled this persistent problem in the pharmaceutical sector.[10]

Drug nanocrystals may be produced by either building up particles from a solution referred to as the bottom-up technique by reducing particle size referred to as top-down approach The first approaches the bottom-up approach is Anti -solvent techniques. Dissolve the drug into a solvent and add it to a nonsolvent solution this approach allows the medicine begins dissolves as tiny pieces in the presence of a stabilizer. Bottom-up technology is the term used to describe the traditional precipitation techniques.

The most often used top-down method is media milling another top-down method is high-pressure

homogenisation. Yttrium stabilized zirconium beads are one kind of milling medium that is used to crush a medication suspension with a stabiliser in water to make nanosuspensions. However, solid oral dose forms are often favoured over liquid ones due to patient convenience and physical stability. Rapid dissolution is the main objective of nanoparticulate systems thus in order to prevent impeding the

NANOSUSPENSION

A number of factors including interoperability with solvents stability at ambient temperature, solubility, additives and visibility are critical to the effective formulation of medicines. As a result of drug discovery efforts Lipophilic or slightly unsalable substances make up around 40% of the new chemical entities found to date. Treatment option for medications water poor solubility and low bioavailability include different formulation strategies.[35]

Production of salt micro-ionization, cosolvents or penetration enhancers, surfactant dispersion methods etc. are examples of common approaches. These techniques however, still don't do a great job of making poorly soluble drugs more soluble. Additional tactics include cyclodextrin-containing inclusion complexes, solids dispersion, emulsion and microemulsion methods and vesicular systems like liposomes which work well as vehicles. However, significant disadvantages of these techniques not all drugs may be used with them.[36]

Nanotechnology may be use to overcome some of the shortcomings of the previously stated methodologies. Drug nanoparticles may be produced from drug microparticles or micronized drug powder. Submicron colloidal dispersions containing drug particles that have been scaled at the nanoscale and stabilised by surfactants are known as nanosuspensions. Higher solubility speeds up the absorption of the API and accelerates the achievement of maximal plasma levels.[37]

dissolving process the solid form must break down and respread into individual nanoparticles as soon as possible. The processes of palletisation, granulation, spray drying and lyophilization are used to solidify nanosuspensions. Similar to freeze-drying methods a matrix-former such as lactose, mannitol or sucrose is often added before drying.

This approach is particularly effective for compounds whose poor permeability, solubility or both give formulators a great deal of trouble. Particulate matter that is less soluble may be given intravenously without blocking blood arteries because of the lower particle size. It is also possible to lyophilise these suspensions to create a solid matrix. Beyond this they are superior than liquid formulations.

Figure Image of Nanosuspension

Preparation of Nanosuspension

Compared to alternative techniques for nanosizing insoluble or weakly water-soluble medications the preparation of nanosuspensions is technically straightforward, facile, and less expensive. Comparing this product to traditional colloidal drug carriers, it is more stable.

Bottom-up technique is seen as a traditional approach. Technologies that are top-down are often favoured over those that are bottom-up. Top-down technology is not widely used because of its high cost and difficulty of handling; in contrast, the nanoprecipitation approach is preferred due to its simplicity, cheap cost, and ease of handling.

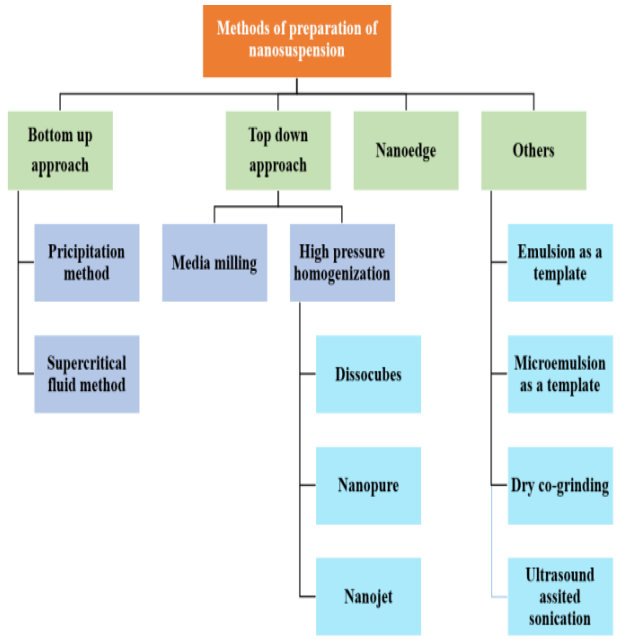

Fig 2.1-Methods of preparation of Nanosuspension

Techniques and Formulation of Nanosuspension

The principle of micro ionization can be applied in media milling or jet milling which are commonly used techniques for preparing nanosuspensions. Micro ionization offers several advantages and disadvantages for instance, it enhances dissolution rates but may limit saturation solubility of the drug. In the following sections both novel and conventional methods for formulating nanosuspensions will be discussed.[40]

Bottom-up Technique

The fundamental concept involves preparing a supersaturated solution of the API which is precipitated into nano-sized particles.

This involves in reducing the solvent gradually to precipitate the API in nano size or solubilizing the drug substance in a medium to induce drug material precipitating in a nanoscale form. 41]

Solvent Anti-solvent Methods

This methodology also known as the precipitation method involves precipitating a solute by adding an anti-solvent. A suitable solvent typically water is used to dispersed the drug substance and form a solution.[42]

The method progresses through two main phases: nuclei formation and crystal growth. To formulate nanosuspensions it is desirable to achieve high nuclei growth and low crystal growth which are temperature dependent Therefore, temperature optimization is crucial in this method. This approach has various of benefits, such as simplicity, Economic viability, scalability, ease of deployment.[43]

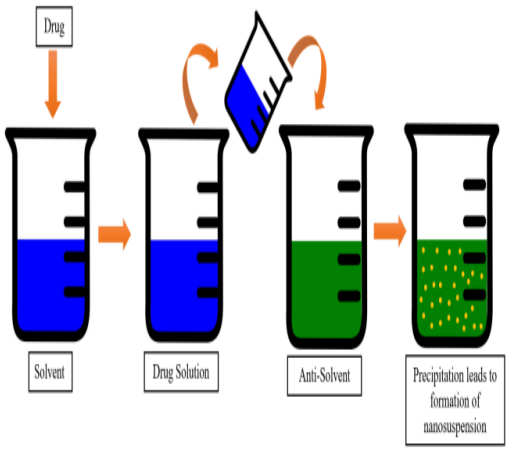

Fig 2.2 Solvent Anti-Solvent Method

2.3.3.2 Supercritical Fluid Method

SFM is one whose critical pressure and temperature are greater than predetermined limits. The supercritical fluid has a diffusivity akin to gases and a density comparable to that of a liquid. Nanosuspensions may be made using methods like Supercritical Anti-solvent, PCA, and RESS. The procedure involves quickly expanding the supercritical fluid containing the API in an appropriate solvent by passing it via a jet.

Supercritical carbon dioxide is use in the precipitation with PCA to create nanoparticle. Due to this technique, the medication mixture is injected, that was compacted by CO2 in it. When the solvable is withdrawn, exceeding saturation leads to precipitation. Among its advantages are its lack of organic solvents and ease of purification for precipitated nanoparticles. [44]

2.3.4 Top-down Technique

This approach is used to implement the disintegration technique. The top-down strategy includes techniques like emulsion diffusion, melt emulsification, high-pressure homogenisation and media milling. By using this technique big particles are reduced to nanosized ones.[45]

2.3.4.1 Media Milling

Liversidge et al. invented this method in 1992, and "Nano system" patented it in the same year. Currently, the patent is held by Drug Delivery.

Controlled temperature conditions are used throughout the process because a high shear rate can cause an increase in temperature which may degrade the heat-labile drug substance as well as excipients.

A "High Shear Media Mill" and "Pearl Mill" is use for media milling. Size reduction in pearl mill occurs because of stagnation which reduces particle size on the nanoscale. Continuous production is possible in a media mill because it is connected to the recirculation chamber. Both batch and continuous mode operation are advantages of this method. [46]

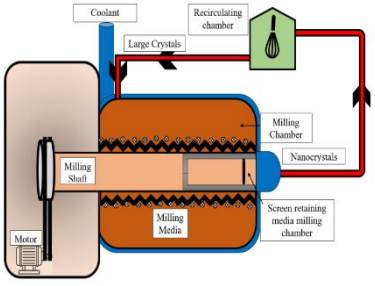

Fig 2.3 Media milling

2.3.4.2 High-Pressure Homogenization

The patent for this procedure is presently held by Skype Pharmaceutical. R. H. Muller discovered the process and the patent was originally owned by DDS GmbH. Three high-pressure homogenizers are generally used the APV Micron Lab 40, the piston-gap homogenizer and the Stansted homogenizer.

Pressure up to 100 to 1500 bar is used in HPH which changes the size of particles from microns to nanoscale by the collision mechanism.[47]

performed in batch or continuous mode with a capacity ranging from just a few milli liters to hundreds of liters The figure 3 indicates the overall process of high-pressure homogenization. The medication and surfactant are initially produced as a micro-sized suspension in an appropriate dispersion me medium. [48]

High pressure is used to drive this dispersion through the homogenizer's small valve hole. Cavitiation forces of particulate are suitable enough to change micron-sized particles into nano size. This method needs preparation of micro suspension to feed into the homogenizer.

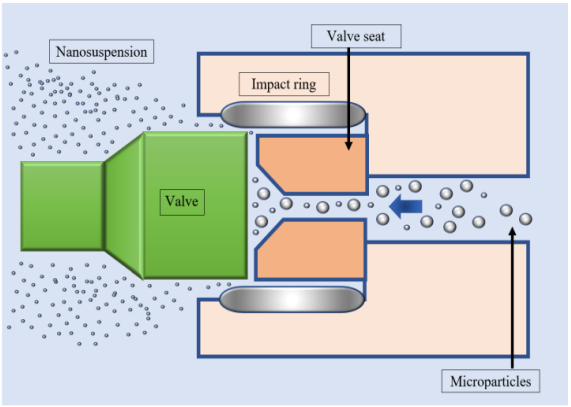

Fig 2.4 High-Pressure Homogenization

2.3.4.3 Nanopure

Due to the low temperatures involved the procedure is often referred to as the Deep-freeze method Typically, the procedure is carried out at 0 degrees Celsius or lower.

2.3.4.4 Nanojet

The collision principle is the foundation of the technique. The Microfluidizers Nanojet M110L and M110S are among the devices that utilize this concept. To produce nanosuspension up to 75 passes are required but the product may still contain a relatively large amount of microparticles.[49]

2.2.3.5 Nanoedge

The Nanoedge technique involves homogenization as well as precipitation. Homogenization reduces crystal formation and increases long-term consistency, which are the main demerit of ppt. In this method, an organic solvent is used to dissolve the API, and this mixture is mixed with the proper anti-solvent, making the API intractable. Drugs particles precipitate as a result. Homogenization is carried out simultaneously with precipitation. [50]

2.2.4 Other Methods

The use of microemulsion as a template, the use of emulsion as a template and co-grinding in a dry state are some other methods used for the preparation of nanosuspension.

2.2.4.1 Emulsion as a Template

The preparation of nanosuspension one can utilize a gel as a model. Using this technique preparation of the emulsion is carried out by dispersing the API in

these solvents. There are two methods for creating NS using the emulsion as an outline approach.51]

First, APIs are solubilized in solvents, and after that, the aq. phase is mixed with the suitable emulsifying agent to form an emulsion.

Surfactant is required for the prompt production of nanosuspension. through the adjustment of surfactant content. This method restricted usefulness for creating nanosuspensions stems from the usage of volatile and toxic solvents including methylene chloride and chloroform.[52]

2.3.4.2 Microemulsion as a Template

A biphasic dosage that is thermodynamically stable is called a microemulsion. O/W microemulsions are recommended for this approach of creating nanosuspension. Suitable surfactant to co-surfactant ratio can be chosen for the required drug loading in the nanosuspension. This method requires further exploration in the future.[54]

2.3.4.3 Dry Co-grinding

Wet grinding part of high-pressure homogenization. Similar to wet grinding, dry grinding may be used to prepare nanosuspension. Less expensive procedure that can be carried out without an organic compound. The technique can produce stable amorphous nanocrystals. Advantage of this method is that it increases physicochemical properties due to altered surface properties.[55]

2.3.4.4 Ultrasound-assisted Sono crystallization

This is a new technique for making nanosuspension. Frequency range for the creation of nanosuspension is 20 to 100 kHz. The frequency of usage results in a reduced in PS.

2.3.5 Characterization of Nanosuspension

2.3.5.1 Particle Size Distribution

The best description criteria for the NS are the PS and the width of the PS distribution since they determine physicochemical properties like rigidity, dissolving acceleration, maximum soluble content and even biological performance. Particle size have an effect on the saturation solubility and dissolving velocity. Size of particles decreases with increasing maximum solubility and dissolution efficiency.[56]

2.3.5.2 Zeta Potential

ZP finds whether the nanosuspension is physically rigid. ZP is an indirect indicator of the diffusion layer density that can be used to forecast sustainability over the long run. For an electrostatically stabilised nanosuspension to exhibit outstanding stability, the minimum ZP needed is ±30 mV, whereas a coupled steric and electrostatic stabilization nanosuspension needs a minimal ZP of ±20 mV.

2.3.5.3 Crystal Morphology

The crystalline structure of the nanosuspension may due to the high-pressure homogenisation adopting an amorphous or other polymorphic form. An increased concentration of the amorphous drug fraction might lead to a higher solubility at saturation.[58]

2.3.5.4 Saturation of solubility and dissolution velocity

The dissolving pressure rises with size decrease. One possible explanation for the very small particle size reduction induced increase in solubility might be a shift in interfacial tension that gives higher excess of solubility. [59]

2.3.6 PHARMACEUTICAL APPLICATION OF NANOSUSPENTION

To create various dosage forms for nanosuspensions, post-production processing is used.

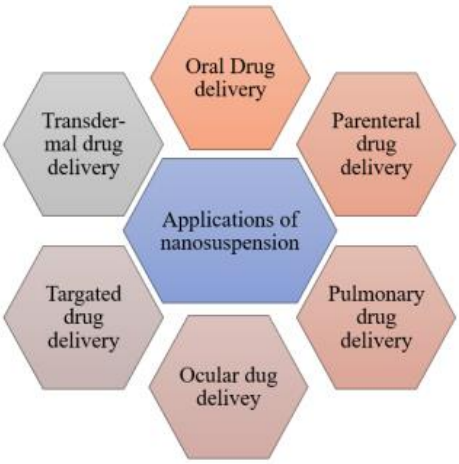

Fig 2.5 Pharmaceutical application of Nanosuspension

- **ORAL DRUG DELIVERY**

Three of the main issues with oral medication delivery are inadequate effectiveness, incomplete dissolution, and poor solubility. The 20% of micronized medicines more than 65% of azithromycin nanosuspensions were observed to disintegrate in 5 hours. Benefits of nanosuspensions include reduced intersubject variability, dosage proportionality, and enhanced oral absorption. Drug nanosuspensions are readily integrated into a variety of dosage forms, by employing normal production procedures. Nanosuspension was effectively added to pellets to provide the medication with a 24-hour sustained release.[60]

- **PARENTRAL DRUG DELIVERY**

Current methods of parenteral distribution include cyclodextrin complexation, salt creation, micellar solutions, solubilisation with cosolvents. However, drawbacks to these techniques, such as low solubilisation capacity, poor parenteral acceptability, expensive production costs, etc. The technique of nanosuspension is employed to tackle these issues. Different parenteral methods, including intra-articular, intraperitoneal, intravenous, etc., are used to give nanosuspensions. Furthermore, parenterally delivered medications become more effective when they are in nanosuspensions. Compared to liposomal clofazimine, clofazimine nanosuspension demonstrated enhanced stability and effectiveness in female mice infected with Mycobacterium avium. According to Rainbow et al intravenous itraconazole nanosuspension improved the antifungal activity in rats more effectively than others forms.[61]

- **PULMONARY DRUG DELIVERY**

Nanosuspensions for pulmonary distribution may be nebulised using mechanical or ultrasonic nebulisers. Because these small particles are so abundant, drug nanoparticles are present in all aerosol droplets. Aqueous medicine solutions are easily nebulised and administered via the pulmonary route because of their minuscule particle size. A variety of nebulisers

may be used to deliver liquid mixes. A number of drugs that have been successfully administered using the pulmonary route. [62]

- **OCULAR DRUG DELIVERY**

Drugs for continuous release are delivered to the eyes using nanosuspensions. Liang and colleagues used Eudragit to create a nanosuspension for ocular administration. The medication was found to be more readily available in the aqueous humour of a rabbit's eye during the experiment. Therefore, the manufacturing of nanosuspensions is a approach to improve the BA and shelf-life of medications after ocular administration.[63]

- **TARGET DRUG DELIVERY**

Because of their surface characteristics, nanosuspensions may be used to target certain organs. Furthermore, it is simple to modify in vivo behaviour by adjusting the stabiliser. The mononuclear phagocytic system will absorb the medication, enabling delivery of the medication to specified regions.

Antifungal, antimycobacterial, or antileishmanial drugs may be directed at macrophages if the infections persist inside the cells. Kayser's invention of an aphidicolin nanosuspension enhance the medication targeting to macrophages infection. This is said that the drug's EC50 in its traditional form.

- **TRANSDERMAL DRUG DELIVERY**

This delivery of the transdermal medications is heavily reliant on penetration through the skin barrier. Reducing particle size to the nanoscale enhances drug penetration through the skin, yielding a higher impact. In non-ionic surfactant-coated nanosuspension, methotrexate demonstrated 2-3 times more transdermal effectiveness compared to the control.[65]

CONCLUTION

One unique and practically viable method for addressing the issues associated with hydrophobic drugs such as poor solubility and low bioavailability High-pressure homogenization and medium milling have proven to be effective methods for producing nanosuspensions on a wide scale. Nanosuspensions for different routes of administration has expanded due to its striking properties which include enhanced bio adhesivity, greater saturation solubility, improved dissolving velocity, variety in surface modification, and ease of postproduction processing. While applications in pulmonary and ocular distribution still need to be assessed, the uses of nanosuspensions in oral and parental routes have been well established. Their topical, nasal, and buccal administration, however, has not yet been completed.

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