Nanosuspension -A Systemic Approaches In Drug Delivery System

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Abstract

The enormous potential of nanometer-sized materials as a medication delivery system with a variety of applications is driving up interest in their manufacture and use. Because they are more affordable and technically straightforward than liposomes and other colloidal drug carriers, nanoscale systems have recently attracted a lot of attention as a means of resolving solubility difficulties. In comparison to other methods now on the market, nanosuspensions have shown to be more effective in increasing the bioavailability of a variety of medications with limited solubility. Parenteral, oral, pulmonary, and topical nanosuspensions have undergone substantial development for a variety of medications and have been tested for in vitro and in vivo applications. They have also been employed to target drug consumption. There are several preparation techniques for nanosuspensions that are being published and patented. In comparison to other nanotechnology-based applications, there are more products based on nanosuspension on the market and in clinical trials. Unexpectedly many novel drug candidates produced by drug discovery programmers are water insoluble and hence poorly bioavailable, which forces development attempts to be shelved. It is now possible to save these so-called "brickdust" candidates by converting them into crystalline nanosuspensions.

Keyword: Nanotechnology, Suspension, Nanosuspensions, Liposomes, Oral drug administration, Parenteral dosage form.

1. Introduction on Nanosuspension

Since the majority of biological qualities exhibiting NCEs are poorly water soluble, pharmaceutical businesses are continually looking for innovative methods to acquire an appropriate oral bioavailability [1-3]. Poor solubility and poor permeability of the lead compounds cause low turnout in the development of new molecular entities as drug formulations, and the increasing frequency of poorly water soluble NCEs exhibiting therapeutic activity is of major concern to the development of new formulations in the pharmaceutical industry [4,5].

Recently, a brand-new and innovative drug delivery method has emerged with the development of such medications as nanoscale systems (which have a size below 1 m) [6]. These systems' primary trait is their quick dissolving rate, which improves bioavailability following oral delivery. The purpose of this paper is to evaluate nanosuspensions as a new and promising method for the formulation of pharmaceuticals that are poorly soluble [7-9].

1.1 Need of Nanosuspension

The production of novel pharmaceutical products is significantly hampered by solubility and bioavailability, particularly if the drug is from BCS class II [10]. Pharmaceutical researchers are continually looking for novel approaches to create products with adequate bioavailability, and it has been observed that more than 1/3 of medications have poor water solubility [11].

Many recently created medications exhibit bioavailability issues as a result of their decreased water solubility. The developers are having a lot of problems because of this. Traditional methods for improving solubility are not always effective, particularly when a medication is poorly soluble in both aqueous and non-aqueous solvents. In order to increase the bioavailability of medications that are poorly soluble, nanosuspension technology has thus shown to be a novel and profitable strategy [12-14].

1.2 History [13]

The nanosuspension drug delivery system (DDS) was first described in 1994 by scientist name ***liversidge***, and since then, much research has been done to develop a generic formulation for pharmaceuticals that are poorly soluble.

Fig 1: Liversidge.

1.3 Definition [15-17]

"A medication Nanosuspensions are colloidal dispersions of medication particles that are nanoscale in size and are stabilized by surfactants. In nanosuspensions, the poorly water-soluble medication is suspended in a dispersion without any matrix components".

The solid particles in nanosuspensions typically have a particle-size distribution less than one micron, with an average particle size between 200 and 600 nm. It is manufactured as DDS using appropriate routes for administration via oral, topical, parenteral, ophthalmic, and pulmonary routes. Drug particles lowered to nanoscale in nanosuspensions show excellent benefits.

Fig 2: Image of Nanosuspension.

The development of high throughput screening and combinatorial chemistry over the past few decades has produced a number of prospective therapeutic candidates with outstanding target receptor binding. However, these candidates' fundamentally low water solubility, brought on by their enormous molecular weights and high log P values, prevents further development as an effective dosage form. According to the traditional Noyes-Whitney equation, the high surface area provided by particle size reduction can greatly increase the dissolution rate and bioavailability. In contrast, drug carriers in nanoparticles are either polymeric or lipid colloidal. When a therapeutic molecule has numerous drawbacks that prevent the development of acceptable formulations, such as the inability to produce salt, huge molecular weight and dose, high log P, and melting point, the only option is the nanosuspension approach [11, 18-23].

The intrinsic tendency of cyclodextrin-based molecular complexation in pharmaceutical formulations to increase formulation size due to the enormous molecular weight of the complexing agent is a significant drawback. By keeping the active pharmaceutical ingredients (API) in a crystalline state and enabling them with higher drug loading during formulation creation, nanosuspensions can resolve such specific drug delivery problems related to them [24, 25]. Due to the reduced usage of toxic non-aqueous solvents and extreme pH, accommodating large drug amounts with minimal dose volume provides significant benefits in parenteral and ophthalmic drug delivery systems. Additional benefits include improved stability, prolonged drug release, greater effectiveness via tissue targeting, reduced first pass metabolism, and deep lung deposits [9, 26-28].

Numerous poorly soluble medication nanosuspension products are either available or being developed. These benefits have accelerated the advancement of nanosuspension technology during the past few decades. Despite the complexity of manufacturing, choosing the right unit operation, equipment, and process optimization can more effectively reduce this complexity. The homogeneous particle size that is created by various production procedures is primarily responsible for the stability of the submicron particles that were achieved in the nanosuspension. Throughout the shelf life of a nanosuspension, the particle size must remain constant to prevent spontaneous crystal formation. In order to prevent the presence of variable saturation solubility and, consequently, to prevent any crystal formation caused by the Oswald ripening effect, maintain a constant particle size distribution [12, 16, 29-31].

2. What is nanotechnology?

New science and technology are frequently the result of human dreams and creativity. These aspirations gave rise to the 21st century frontier of nanotechnology. The easiest definition of nanotechnology is "technology at the nanoscale" [32].

Definition: ***"As the science and engineering involved in the design, synthesis, characterization, and use of materials and devices whose smallest functional organisation in at least one dimension is on the nanoscale scale, or one billionth of a meter, we refer to this field as nanotechnology"*** [33, 34].

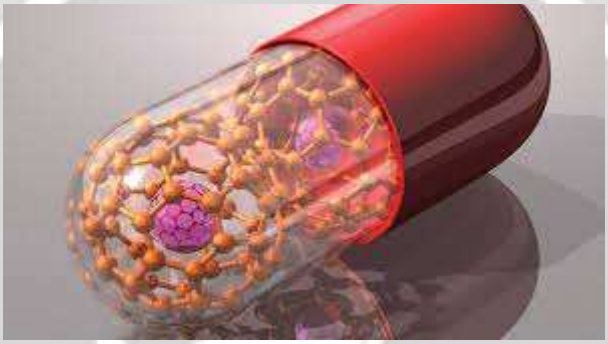

Fig 3: Image on nanotechnology in medicines.

Richard Zsigmondy, the 1925 winner of the Nobel Prize in chemistry, was the one who initially coined the term "nanometer." He was the first to use a microscope to measure the size of particles like gold colloids, and he also invented the term nanometer specifically to describe particle size [36].

The inventor of contemporary nanotechnology is physicist **Richard Feynman**, who won the Nobel Prize in physics in 1965. He proposed the idea of influencing matter at the atomic level in a talk titled "There's Plenty of Room at the Bottom" during the 1959 American Physical Society meeting held at Caltech. With this innovative concept, new methods of thinking were demonstrated, and Feynman's theories were later found to be true. He is regarded as the founding father of contemporary nanotechnology because of these factors [37].

Fig 4(a): Image of Richard Zsigmondy

Fig 4(b): Image of Richard Feynman

The new fields of nanoscience and nanotechnology attracted more attention towards the beginning of the twenty-first century. The prestige of Feynman and his idea of manipulating matter at the atomic level significantly influenced national science priorities in the United States. In a speech delivered on January 21, 2000 at Caltech, President Bill Clinton argued in favour of funding research into this cutting-edge technology. The 21st Century Nanotechnology Research and Development Act was passed into law three years later by President George W. Bush. The National Technology Initiative was established by the Act, which elevated nanotechnology research to a national priority (NNI). The President's Cabinet-level National Science and Technology Council (NSTC) and its Committee on Technology serve as the framework through which the NNI is governed today. The Subcommittee on Nanoscale Science, Engineering, and Technology (NSET), which is made up of officials from 20 US departments and independent organizations and commissions, is in charge of planning, budgeting, implementing, and reviewing the NNI [16, 22, 26, 38-40].

These materials and devices can be created to interact with cells and tissues at a molecular (i.e., subcellular) level with a high degree of functional specificity for applications in medicine and physiology, enabling a level of technological and biological system integration that was previously unachievable. In order to bring together the necessary collective skills needed to develop these revolutionary technologies, traditional sciences such as chemistry, physics, materials science, and biology have come together to form the growing field of nanotechnology [41].

In order to benefit from the enhanced properties of materials at the nanoscale, such as higher strength, lighter weight, increased control of the light spectrum, and greater chemical reactivity than their larger-scale counterparts, scientists and engineers today are developing a wide range of deliberate manufacturing techniques [41].

Several kinds of DDS using nanotechnology principle [41]:

1) Nanosuspension

2) Nanocrystals

3) Solid lipid nanosuspensions

4) Nanoemulsion

3. What is nanomedicine? [7, 33, 42-48]

A new discipline called nanomedicine has emerged as a result of the growing interest in the medicinal uses of nanotechnology. This field uses nanotechnology in medication development and makes ever-exciting claims about new diagnosis and treatments. In 1999, American scientist Robert A. Freitas Jr. published Nanomedicine: Basic Capabilities, the first of two books he devoted to the topic. This is when the phrase "nanomedicine" first appeared.

Nanomedicine is defined as ***"the molecular monitoring, repair, creation, and control of human biological systems using designed nanodevices and nanostructures."***

Nanomedicine applies the principles of nanoscale assembly and manipulation to clinical applications in the medical sciences. The process of using molecular instruments and molecular knowledge of the human body to diagnose, treat, prevent disease and traumatic injury, relieve pain, maintain and improve human health is known as nanomedicine. The use of nanotechnology in medicine is known as nanomedicine. The potential uses of nanotechnology in medicine are vast. It is understood that as particles get smaller, their surface area expands and more atoms and molecules are located on the surface than inside.

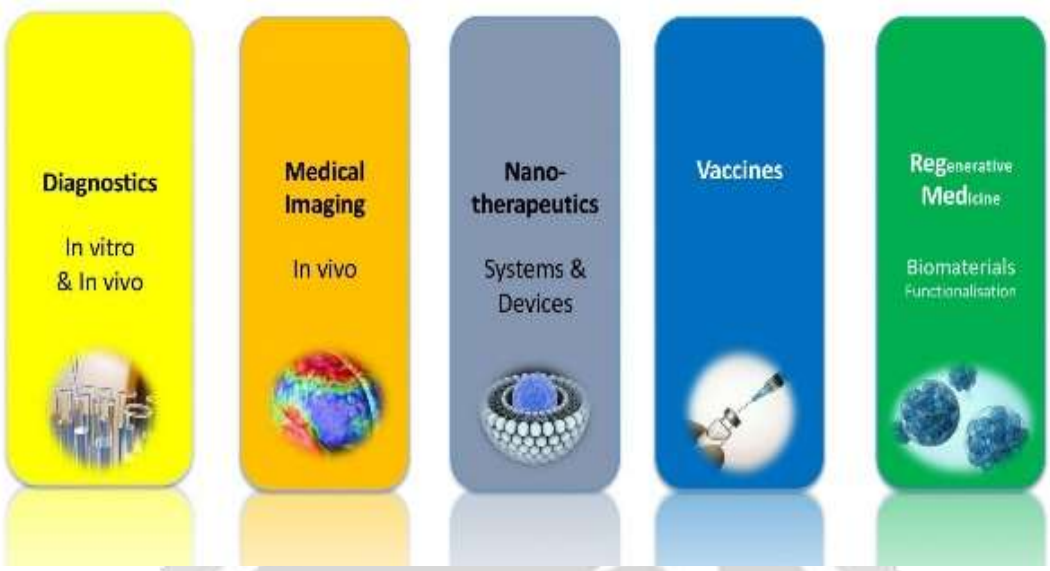

Fig 5: Nanomedicine.

Numerous nanomedical applications have been created, despite the fact that nanomedicine is still in its infancy. The creation of nanocapsules to help cure cancer has also been a focus of research, as well as the development of biosensors to aid in diagnostics and delivery systems for genetic therapy, drugs, and vaccinations.

Particle detection, drug delivery systems, vaccine carriers, emulsions, and nanofabricated biomaterials with extraordinary strengths, hardnesses, low friction, and better biocompatibility are currently the focus of nanomedicine. Future research will focus on more advanced ideas, such as nanomachines that could travel around the body and diagnose and treat microscopic heart or brain abnormalities.

In order to comprehend the structure and operation of biologic devices and to employ nature's answers to progress science and engineering, nanomedicine also seeks to learn from nature. This strategy is known as "biomimicry." Biologic devices, substances, and processes that operate at the nanoscale or molecular level and offer performance that is unmatched by synthetic technology have been created through evolution in an astounding number and variety.

Nanomedicine is a branch of nanotechnology that has attracted interest as a location for international research and development, giving the discipline academic and economic validity. The top nations investing in nanomedicine research are the United States, the United Kingdom, Germany, and Japan. Funding for this research comes from both governmental and commercial sources. These nations are joined in terms of the amount of nanomedicine research by China, France, India, Brazil, Russia, and India.

Nanomedicine, which operates at the molecular level, is energized by claims of the seamless fusion of biology and technology, the elimination of disease through customized medicine, targeted drug delivery, regenerative treatment, and nanomachinery that can replace specific cell parts. Although many of these predictions may not come true, several nanomedicine applications already exist and have the potential to fundamentally alter how medicine is practiced as well as how we currently comprehend health, disease, and biology—aspects that are crucial for modern society. In 2012, the field's global market share reached $78 billion, thanks in large part to technical developments. The market is projected to increase to about $200 billion by the end of the decade.

Fig 6: Image of the various nanomedicine shapes and their approximative sizes are depicted in this illustrated picture. The top of the picture displays the dimensions of biological nanostructures for comparison.

3.1 Development of nanomedicine [49, 50]

The scale on which nanomedicine operates (1 to 100 nm), the size of molecules, and biochemical processes account for a large portion of its rhetorical, technological, and scientific strength. The history of nanomedicine, specifically its ties to molecular medicine and nanotechnology, is another area of discussion. The example of nanotechnology is instructive: on the one hand, supporters of nanomedicine frequently mobilize its potential in terms of science, as well as in terms of funding and recognition; on the other hand, there is an attempt to distance nanomedicine from nanotechnology, out of concern that it will be harmed by the perceived "hype" that surrounds it. The goal is for nanomedicine to develop independently rather than as a branch of nanotechnology.

4. Advantages of Nanosuspension [3, 51-56]

Below is a list of some unique characteristics of nanosuspension that make it a possible medication delivery method.

1) Long physical stability.
2) Decreased particle size.
3) Increased dissolution rate.
4) Increased rate, and extent absorption.
5) Drugs with high log P value can be prepared as nanosuspensions in order to increase their bioavailability.
6) Compounds that are soluble in oil but insoluble in water can be used to create nanosuspension.
7) Extended surface area
8) Continued rate of collapse
9) Less dose measurement is necessary, and the amount of doses
10) Prescriptions are protected from fraud.
11) All medicines have a quicker beginning of action.
12) The medicinal nanosuspension may be administered orally, topically, parenterally, ocularly, pulmonary, etc. As fact, nanosuspensions can be used in suppositories, hydrogels, tablets, and pellets.
13) Due to the drug's high dissolving rate and saturation solubility, it can enhance in vivo performance.
14) Manufacturing simplicity and scaling up for massive output.
15) The potential for surface alteration to facilitate drug delivery at a particular spot.
16) The amorphous proportion of the particles can be increased via nanosuspension technology, which could modify the crystalline structure and solubility.
17) Reduced tissue irritancy whether administered subcutaneously or intramuscularly.
18) By reducing the particle size, the medications' absorption from their absorption window may be boosted.

5. Disadvantages of Nanosuspension [57-60]

1) Physical stability, sedimentation, and compaction are three factors that might lead to difficulties.
2) It is bulky, thus proper care must be given when handling and transporting it.
3) Inadequate dose.
4) Standardized and precise doses cannot be applied simultaneously.

6. Preparation of Nanosuspension

Nanosuspension in liquid DDS is a liquid colloidal dispersion of stabilisers, liquid dissolution medium, and drug nanoparticles with an average size less than 1000 nm. Polymer surfactants called stabilisers are used to keep a nanosuspension stable. Water, aqueous solutions, nonaqueous solutions, or organic solvents can all be used as liquid dissolution media. The crystalline structure and particle size of the drug nanoparticle can both have an impact on its saturation solubility. Temperature and other parameters, such as the dissolution medium, also come into play. When the size of the drug particles decreases below the size of 1 m, the Kelvin and Ostwald-Freundlich equations state that the saturation solubility increases with the decrease of particle size. Reducing the size of drug particles also increases surface area, hastening the rate of dissolution and enhancing bioavailability. The Nernst-Brunner and Levich adaptation of the Noyes-Whitney equation can account for this [61-63].

The liquid nanosuspension DDS has been prepared using a variety of fabrication procedures used by research labs and pharmaceutical specialists. Those methods are classified into 4 categories:

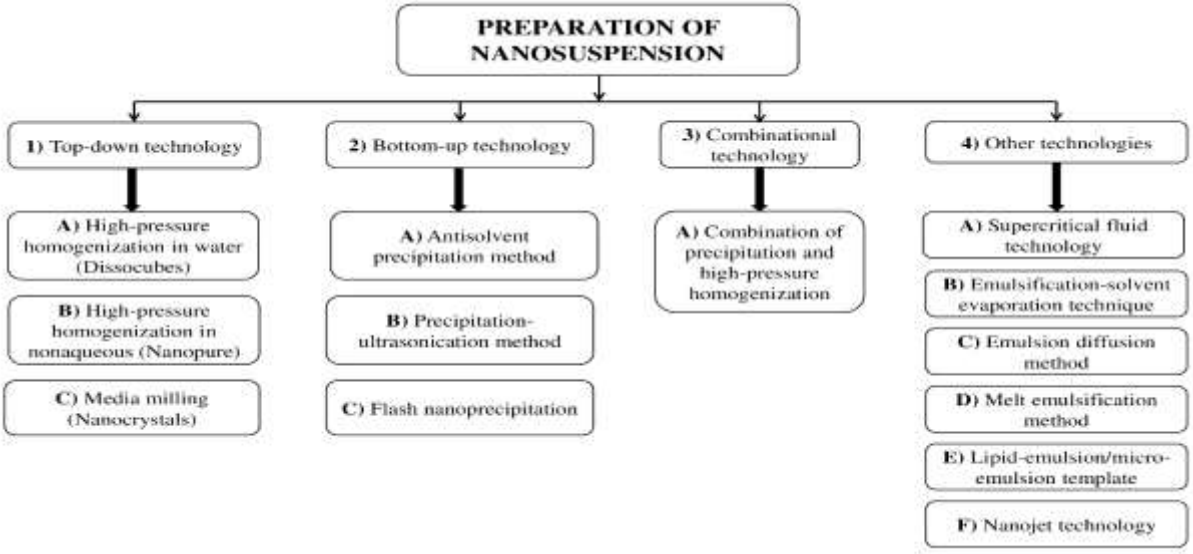

Fig 7: Image of preparation of nanosuspension.

6.1 Top-down technology

Large drug crystals shrink into the micrometer range in top-down technology before shrinking further into the nanodimension in a stabiliser solution. The high-energy procedure known as high-pressure homogenization and the low-energy process known as media milling are the two main techniques used in top-down technology [64].

6.1.1 High-pressure homogenization

Drugs that are poorly soluble are frequently prepared into nanosuspensions using high pressure homogenization.

The two different high-pressure homogenization techniques are:

6.1.1.1 High-pressure homogenization in water (Dissocubes)

R. H. Muller invented the Disso Cubes technology (Muller et al. 1998). Disso Cubes' patent rights were formerly owned by DDS (Drug Delivery Services) GmbH, however SkyePharma plc now has those rights. High-pressure homogenizers of the piston-gap type are used in the design of Disso Cubes. The APV Micron LAB 40 (APV Deutschland GmbH, Lubeck, Germany) is a widely used homogenizer. It is possible to employ alternative piston-gap homogenizers made by Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd, Stansted, UK). A high-pressure plunger pump and a relief valve make up a high-pressure homogenizer. (Homogenizing valve). The plunger pump's job is to supply the energy needed for the relief. A fixed valve seat and an adjustable valve make up the relief valve. Together, they provide a radial precision gap that is movable. As a result of the force operating on the valve, the gap conditions, resistance, and consequently the homogenising pressure change [28, 13, 65-67].

Dissocube homogenization takes place in aqueous media. A suspension is driven through a small aperture in the dissocubes process when a pressure of up to 1500 bar is applied. The water may boil at room temperature as a result of the dynamic pressure increasing and the static pressure decreasing as a result. There will be a lot of gas bubbles produced when water boils at normal temperature. Once the suspension has left the space and the pressure has returned to atmospheric levels, the gas bubbles will implode in a phenomenon known as cavitation. The drug particles break up into nano-sized fragments as a result of implosion, collisions, and strong shear. The physical properties of the resulting nanosuspensions, such as the particle size distribution, may be influenced by factors such as drug particle hardness, number of homogenization cycles, homogenization pressure applied, and temperature [68-70].

The Dissocubes technique demonstrates a number of benefits. No materials that had been treated experienced erosion. By managing drug quantities ranging from 1 mg/mL to 400mg/mL, nanosuspensions with exceptionally low and high concentrations can be created. Additionally, it enables the aseptic manufacturing of parenterally administered nanosuspensions. Even less than 1 ppm of metal contamination can be detected after 20 cycles of homogenization when a high pressure of 1500 bar is used. The main drawback of this approach is that numerous cycles of pretreatment and homogenization are required in order to obtain microparticles prior to the homogenization procedure. The high cost of the equipment, which will raise the price of dose formation, is another disadvantage [71].

6.1.1.2 High-pressure homogenization in nonaqueous (Nanopure) [22, 9, 62, 72-77]

Nanopure is homogenised in nonaqueous or combinations of aqueous fluids. The low-temperature Nanopure procedure, often known as the deep-freeze method, is another high-pressure homogenization technique. Due to the low vapour pressure of oils or oily fatty acids and their high boiling point, cavitation cannot develop when drug nanocrystals are disseminated in water mixes or nonaqueous media. The drug nanosuspensions in the nonaqueous media were homogenised at 0° C or below the freezing point as a result of insufficient pressure reduction. Thus, thermo-labile chemicals can be processed using the Nanopure method. Additionally, the outcomes of the Nanopure procedure are on par with those of the dissocubes technique.

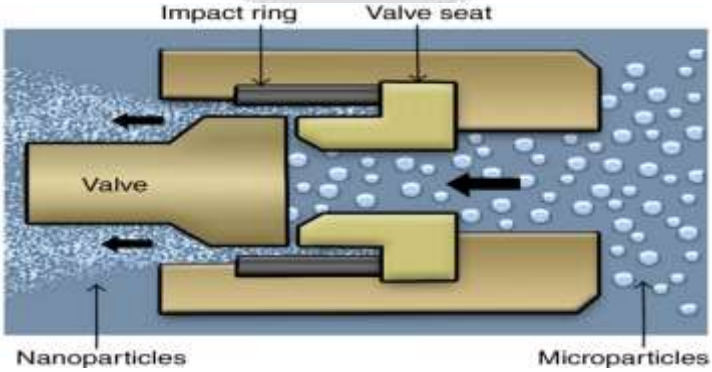

Fig 8: Image of Nanoscale High-pressure homogenization in nonaqueous (Nanopure)

Effect of homogenization pressure: Homogenization pressure's impact. The effect of the homogenization pressure on the particle size should be examined in each situation in order to optimize the process parameters because the homogenizer can handle pressures ranging from 100 to 1500 bars. It is anticipated that the resultant particle size will be smaller the greater the homogenization pressure. According to research done on RMKP 22, 4-[N-(2-hydroxy-2-methyl-propyl)-ethanolamino]-2,7-bis(cis-2,6-dimethylmorpholin-4-yl)-6-phenyl-pteridine, there is an inverse correlation between the homogenization pressure and the particle size.

Number of homogenization cycles: cycle count for homogenization. In many cases, a single homogenization cycle is insufficient to produce the necessary particle size. Usually, several cycles are needed. Therefore, homogenization can be done in three, five, or ten cycles, depending on the drug's hardness, the intended mean particle size, and the needed homogeneity of the result. It is expected that the particle size would decrease the more homogenization cycles there are. After each cycle of homogenization, the drug's particle size and polydispersity index may be analysed to determine the ideal number of cycles.

Advantages of High-pressure homogenization

1) It is simple to synthesise medications into nanosuspensions, even if they are poorly soluble in organic and aqueous environments.
2) Scale-up is simple, and there is little batch-to-batch variance.
3) the drug's nanoparticulate particles have a restricted size distribution in the finished product.
4) produces nanosuspensions for parenteral delivery in an aseptic manner.
5) flexibility in managing the drug amount, from 1 to 400 mg mL1, allowing for the synthesis of both highly concentrated and very diluted nanosuspensions.

Disadvantages of High-pressure homogenization

1) Micronized medication particles are required.
2) It must first be formed into a suspension using high-speed mixers before being homogenised.

6.1.2 Media milling [78-81]

In 1992, Liversidge made the discovery of the media milling technique. This technique uses high-shear media mills or pearl mills to produce nanosuspension. In Fig., the standard media mill is depicted.

The drug particles are dispersed into nanoparticles during the shearing process. Additionally, continuous output is maintained because of its link to the recirculating chamber. This approach is more appealing since it uses less energy, is simple to scale up, has little batch to batch fluctuation, can handle vast amounts of material, and has four FDA-approved medications.

Principle:

Media milling can be used for batch or continuous operations, and it can reduce particle size to less than 200 nm in 30 to 60 minutes. The milling media or balls are often constructed of ceramic-sintered aluminium oxide or rigid polystyrene resin. Drug nanoparticles are created by friction and collisions between the milling media, which are pearls, and the aqueous suspension of the drug and stabiliser in the milling chamber. Shearing can be done at a temperature that is controlled despite the heat that it can produce. The key benefits of media milling also include easy scale-up and slight batch-to-batch variation. But using this technique can lead to the erosion of pearls that could taint the drug nanoparticle result.

Advantages of media milling [82, 83]

1) It is simple to synthesise medications into nanosuspensions, even if they are poorly soluble in organic and aqueous environments.
2) Simple scaling up and little fluctuation from batch to batch.
3) A final nanosized product with a narrow size dispersion.

4) The drug dosage can be handled with flexibility, ranging from 1 to 400 mg/mL, allowing the production of both highly concentrated and very diluted nanosuspensions.

Disadvantages of media milling

1) With the introduction of milling medium based on polystyrene resin, the severity of this issue has been significantly diminished. The normal residual monomer concentration for this medium is 50 ppb, and the residuals produced during the milling processes do not exceed 0.005% w/w of the finished good or the ensuing solid dosage form.
2) Erosion from milling material might lead to product contamination.
3) The process's duration is not conducive to production.
4) Germ growth in the water phase when milling for an extended period of time.
5) Time and expenses related with the milling material separation technique from the medication nanoparticle solution, particularly for generating parenteral sterile products.

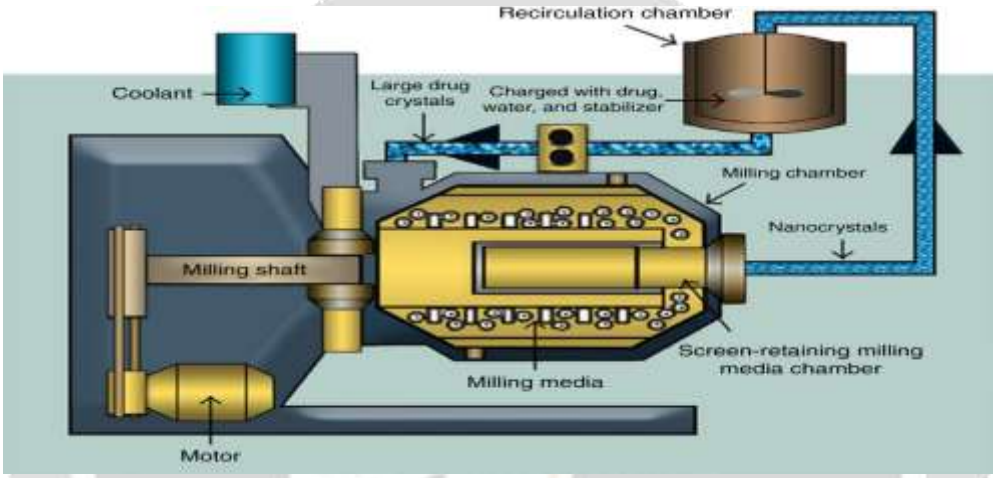

Fig 9: Image of Media milling.

6.2 Bottom-up technology [84-86]

The medication is typically dissolved in an organic solvent during the bottom-up procedure, and an antisolvent is then added to create precipitation in the presence of a stabiliser.

By starting at the molecule level and progressing to solid particle formation through molecular association, this term means that traditional precipitation techniques are addressed by lowering the solvent's consistency, such as by pouring a solvent into a non-solvent or raising the temperature, or a combination of the two. Precipitation-ultrasonication and antisolvent precipitation are two frequently used bottom-up approaches.

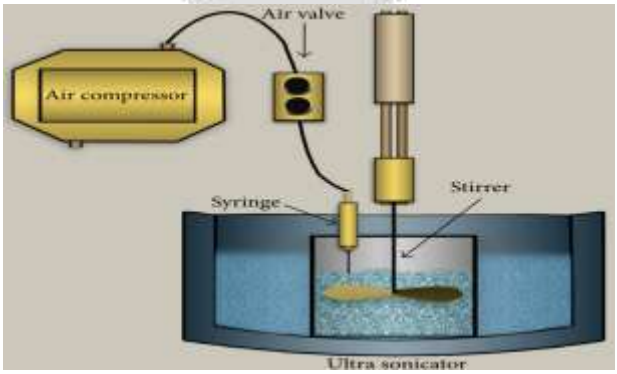

Fig 10: Image of Bottom-up technology.

6.2.1 Antisolvent precipitation method

Drug particles in the micro- and nano-size range are prepared via antisolvent precipitation. In most cases, the antisolvent is swiftly added while still being in the presence of a surfactant after the medicine has been well dissolved in a solvent. Rapid drug precipitate production causes a quick supersaturation of the drug in the combined solution, resulting in the development of ultrafine crystalline or amorphous drug nanoparticles. There are two stages to this process: crystal growth and nuclei production. The particle size distribution of nanocrystals generated under supersaturation conditions is typically wide. Considerations such as the ratio of organic solvent to antisolvent, the rate at which antisolvent is added, the concentration of drug precursors, the temperature at which nanoparticle formation occurs, and the stabiliser used should all be made in order to prepare nanosuspension with the desired particle size distribution. The stabiliser used should have strong affinity to the particle surface and a high diffusivity to quickly cover the freshly created surface in order to produce a more stable nanosuspension. Additionally, there ought to be enough stabiliser to thoroughly cover the particle's surface. The production of nanoparticles is influenced by temperature, which alters the size distribution. Generally speaking, when temperature rises, drug solubility rises, supersaturation levels fall, and there are fewer crystallisation particles accessible. The increase in solute molecules that results will help the nanocrystal develop quickly.

6.2.2 Precipitation-ultrasonication method [37, 87-89]

Due to the fact that ultrasound irradiation can encourage molecular movement and mass transfer, ultrasonication has recently been developed as a successful method for managing the crystallisation process. It was discovered that by merely raising the applied ultrasonic power, the crystal size may be decreased. Nevertheless, no discernible change in particle size was seen when the ultrasonic power input was between 400 and 580 W. Thus, 400 W of power input is sufficient to accomplish the best particle size reduction. The length of time the drug particle is exposed to ultrasonication also affects the size of the nanoparticles. When the ultrasonication period was increased to 15 minutes, it was discovered that the particle size was greatly reduced. However, even using a longer sonication period, no discernible difference in particle size was seen. The ideal amount of time to create nanosuspension is thus 15 minutes. Additionally, by applying ultrasonication to a milling solution, the polydispersity index and the quality of the nanoparticles may be considerably enhanced.

6.2.3 Flash nanoprecipitation [57, 85, 90-93]

Recently, a bottom-up method called flash nanoprecipitation (FNP) has been devised to create organic nanoparticles. Both multi-inlet vortex mixers (MIVMs) and confined impinging jet mixers (CIJMs) are made to efficiently mix every component of the solvent mixture. The creation of nanoparticles is often accelerated by the fast solute precipitation and increased supersaturation level in flash nanoprecipitation. Typically, CIJM may effectively enhance the product conversion when used as a technique to accomplish FNP. However, in this procedure, the antisolvent streams must have similar momenta and equivalent volumetric flow rates. The accumulation of the supersaturation level inside the mixer has been constrained by this criterion.

MIVM is created for FNP to accomplish quick micromixing, convenience of use, and scaling up in order to overcome the constraint of CIJM. By combining each stream with the momentum, MIVMs may micromix themselves. In the four-stream MIVM, mixing of streams with different volumetric fluxes is permitted. Additionally, by adjusting the volume and flow rate of each separate stream, the supersaturation and solvent composition may be adjusted. As a result, even when certain streams are flowing at large volumes and the others are flowing at low volumes, adequate micromixing of the streams may still be achieved. Additionally, MIVM may be used to create nanoparticles with a variety of active species, and the stability of the final particles can be adjusted by adjusting the solvent/antisolvent input ratios. In order to create nanoparticles with a regulated size distribution and a high DLR, the conditions of fast micromixing and high supersaturation levels can be used.

Advantages of Bottom-up technology

1) Equipment is employed that is inexpensive and basic.

2) The benefit of precipitation over other nanosuspension production techniques is higher solubility in saturation.

Disadvantages of Bottom-up technology

1) The drug must at the very least demonstrate solubility in one solvent.
2) A solvent must be miscible with at least one non-solvent.
3) Because solvent residues must be removed, production costs go up.
4) It might be challenging to keep the particle character intact (i.e., size, especially the amorphous fraction).
5) Additionally, it does not apply to the medications since they have a low solubility in both aqueous and non-aqueous systems.

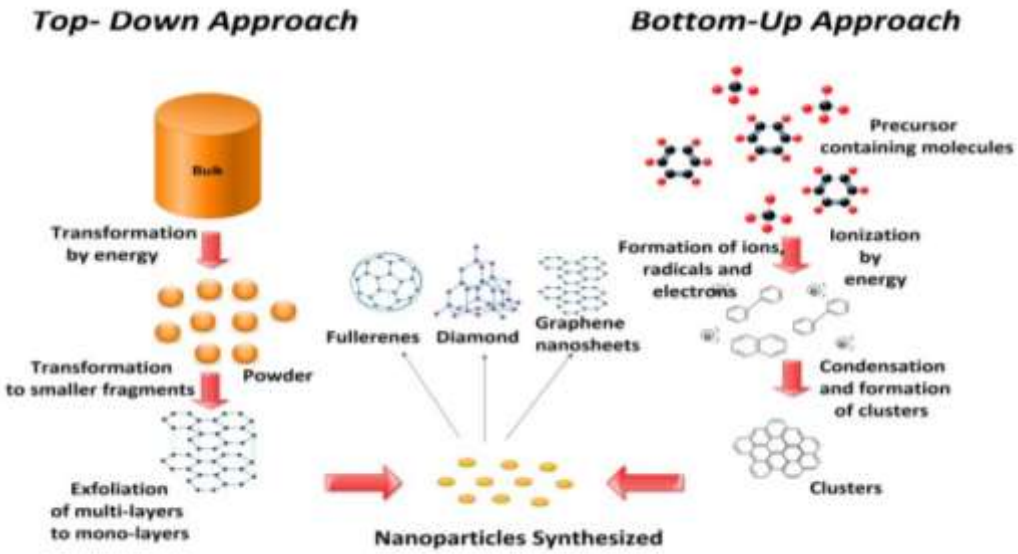

Fig 11: Image of Flash nanoprecipitation.

6.3 Combination technology [77, 14, 94-96]

Precipitation is a typical bottom-up procedure that the combination technology goes through before a top-down process like high-pressure homogenization.

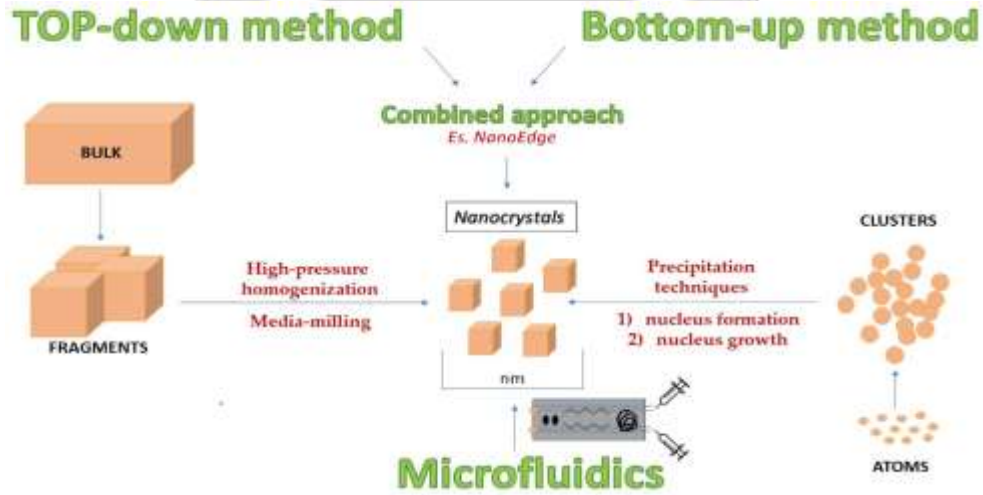

Fig 12: Image of Combination technology

6.3.1 Nanoedge technology

Integrated technology known as NANOEDGE is widely used, and Baxter International, Inc. has registered it as a trademark with serial number 76322804. NANOEDGE is made to make water-insoluble medicines effective therapeutic agents. A better particle size distribution and greater stability are often achieved by combining precipitation and homogenization processes. Precipitation is carried out using water-miscible solvents such methanol, ethanol, and isopropanol. Even if a very little amount of solvent is permitted during the formulation process, it is still important to eliminate the solvents that remain in the precipitate. The NANOEDGE technique, on the other hand, incorporates an evaporation stage to produce beginning material devoid of solvent, which is then treated by high-pressure homogenization**.** Both the precipitation technique's and the homogenization technology's shortcomings may be fixed by using NANOEDGE technology. The precipitated suspension is further homogenised in the NANOEDGE technique, which reduces the particle size and prevents further crystal development. The homogenization stage checks the crystal development of the nanoparticles, resulting in particles in the nano range with enhanced thermodynamics.

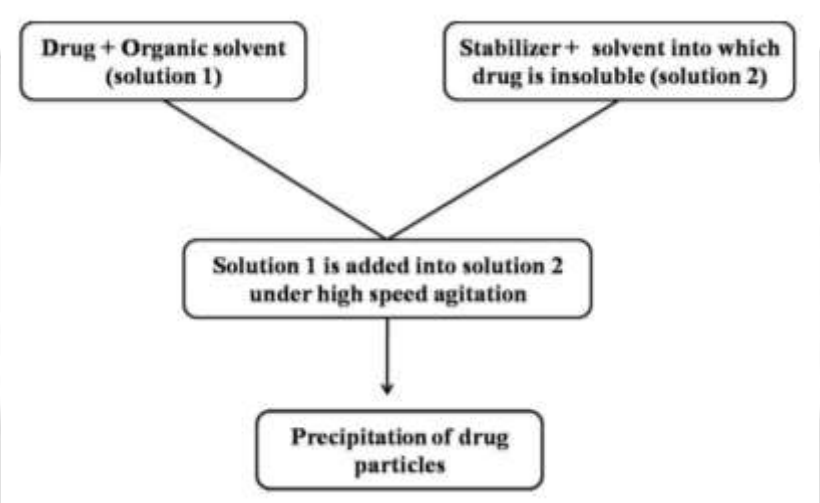

Fig 13: Image of Nanoedge technology

6.4 Other technologies

6.4.1 Supercritical fluid technology [29, 97, 98]

Nanoparticles made from pharmacological solutions are frequently manufactured using supercritical fluid technology. There are several techniques that may be used, such as the supercritical solution process (RESS), the supercritical antisolvent process, and the precipitation with compressed antisolvent process (PCA). The RESS technique involves expanding the drug solution in supercritical fluid using a nozzle, which reduces the supercritical fluid's solvent power and causes the drug to precipitate as tiny particles. This technique was said to have produced cyclosporine nanoparticles between 400 and 700 nm in size. The medication solution is atomized into a chamber with compressed carbon dioxide when using the PCA technique. After the solvent is removed, the solution becomes supersaturated and fine crystals precipitate out. A supercritical fluid that is poorly soluble in a medication is utilised in the supercritical antisolvent method. A solvent that is miscible with the supercritical fluid is used to dissolve the medication. The medication solution becomes supersaturated after being injected into the supercritical fluid, which then completely removes the solvent. The medication will then crystallise into tiny particles. The majority of the solvents used in the procedures outlined are dangerous, which is their main disadvantage when compared to

alternative approaches. Additionally, a lot of stabilisers and surfactants are utilised in the preparation process.

Disadvantages of supercritical fluid technology

1) In comparison to other approaches, toxic solvents are used, as are significant amounts of surfactants and stabilisers.
2) Overgrowth of particle nucleation owing to brief high super saturation, which may also result in the formation of an amorphous polymorph or another undesirable polymorph.

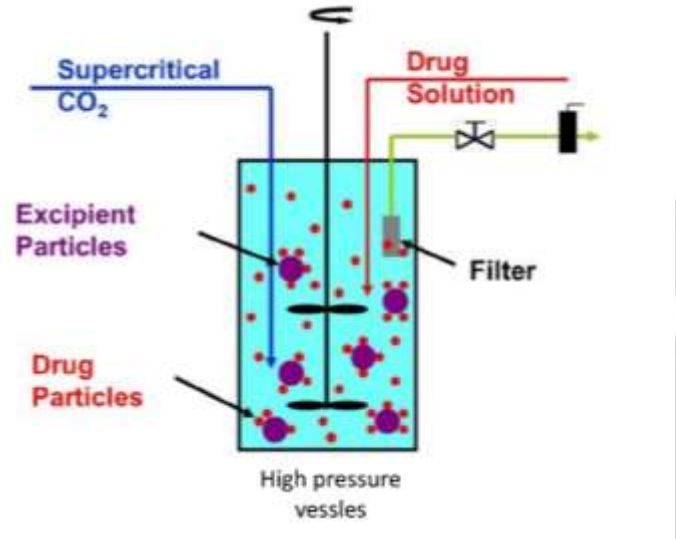

Fig 14: Image of Supercritical fluid technology.

6.4.2 Emulsification-solvent evaporation technique [89, 99-102]

The drug solution is initially created in the emulsification-solvent evaporation process. The medication was then just marginally soluble in another liquid, which was used to conduct the emulsification. The drug nanocrystals precipitate out once the solvent has completely evaporated. By generating high-shear forces, the high-speed stirrer may be used to control crystal development and particle aggregation.

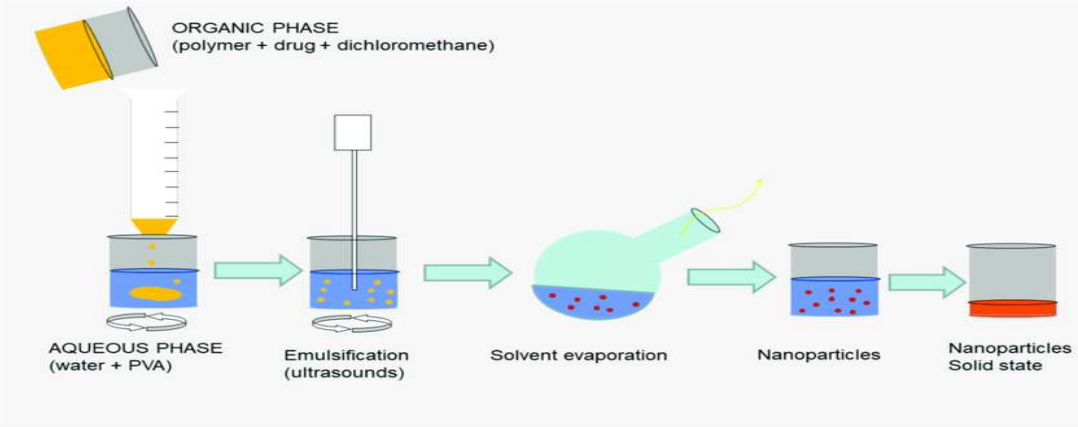

Fig 15: Emulsification-solvent evaporation technique.

6.4.3 Emulsion diffusion method [103]

The emulsion may be used as a template to create nanosuspensions in addition to serving as a medication delivery system. Using the emulsion diffusion approach, medicines that are somewhat water-miscible and soluble in volatile organic solvents can be tested. The organic solvent or a combination of solvents dissolves the medication particles. After that, an emulsion is created by swirling the organic solution into an appropriate aqueous phase that also contains surfactants. After obtaining the emulsion, high-pressure homogenization is frequently used to further homogenise it. To dissipate the organic solvent after homogenization, the emulsion was first diluted with water and then homogenised using a homogenizer. Next, the droplets were transformed into solid particles. Since one particle is created in each emulsion droplet, the size of the emulsion droplet may be adjusted to adjust the nanosuspension's particle size. Methanol, ethanol, ethyl acetate, and chloroform are frequently utilised as the organic solvents in the emulsion diffusion technique.

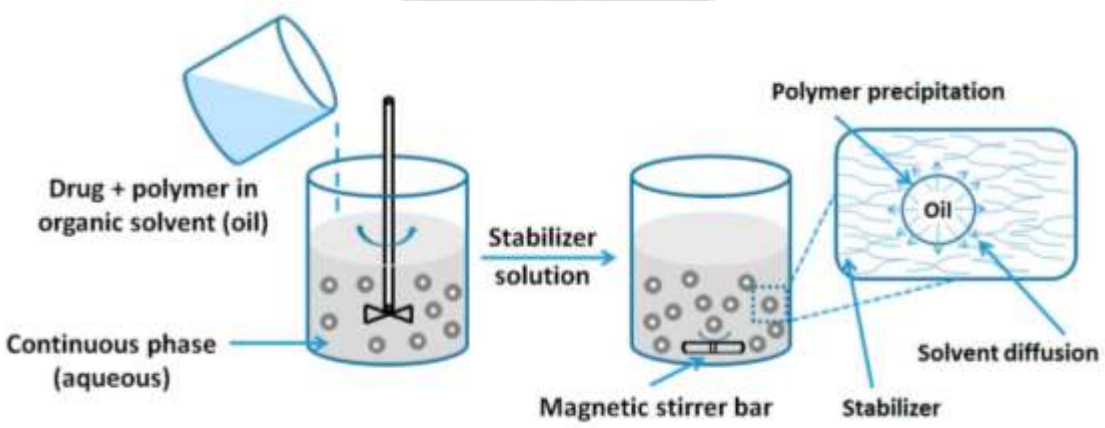

Fig 16(a): Image of Emulsion diffusion method.

Advantages of emulsion diffusion method

1) It is not essential to use specialist equipment.
2) Particle size may be readily changed by adjusting the emulsion droplet size.
3) Ease of scale-up if the formulation is correctly tuned.

Disadvantages of emulsion diffusion method

1) This approach cannot be used to create drugs that are poorly soluble in both aqueous and organic environments.
2) Because of the usage of dangerous solvents in the process, there are safety issues.
3) Diultrafiltration is required for the purification of the drug Nanosuspension, which may make the process expensive.
4) Stabilizers and surfactants must be used in high quantities throughout the manufacture process.
5) In comparison to the previous manufacturing procedures, a large amount of surfactant/stabilizer is required.

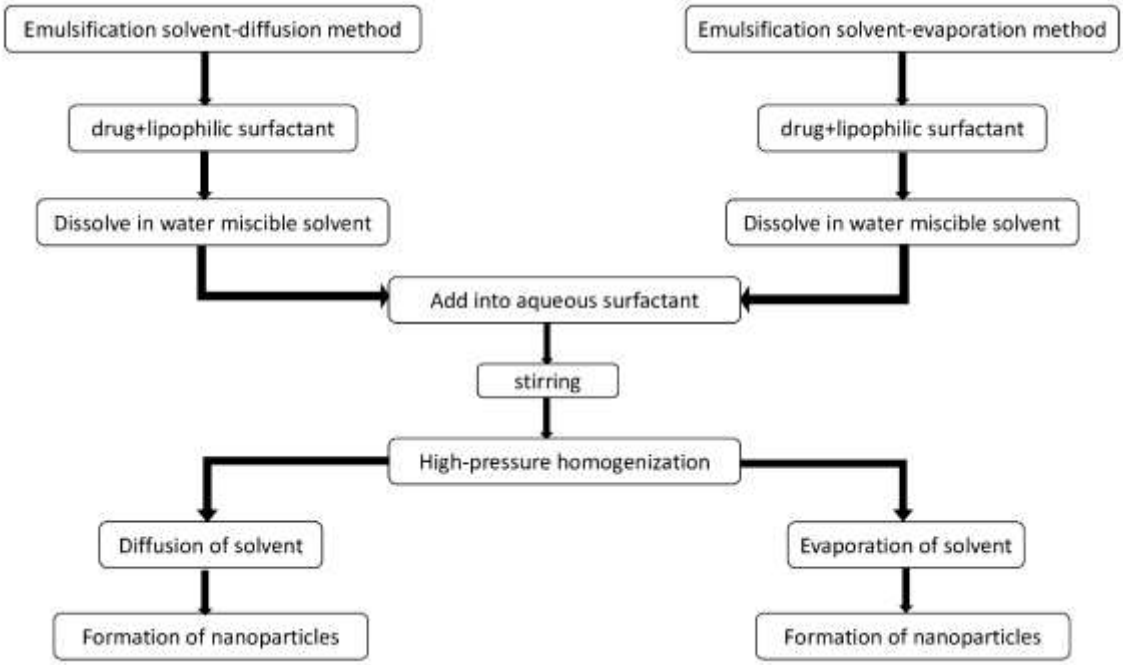

Fig 16(b): Image of Emulsion diffusion method.

6.4.4 Melt emulsification method [92, 96, 104-106]

The drug substance is initially disseminated in the aqueous solution with stabiliser in the melt emulsification technique. The solution was then heated to a temperature above the drug's melting point and homogenised to produce an emulsion. The emulsion was kept warm enough to be above the drug's melting point during this procedure. The drug emulsion was then gradually chilled to room temperature or put into an ice bath. The concentration of the medication, the quantity and kind of stabilisers employed, the cooling temperature, and the homogenization procedure are the key determinants of nanosuspension particle size. According to a report, ibuprofen nanosuspension made using the melt-emulsification method disintegrates more quickly than nanosuspension made using the solvent-diffusion method.

Advantages of melt emulsification method

1) In comparison to the solvent diffusion approach, the melt emulsification technology completely forgoes the use of organic solvents during manufacture.

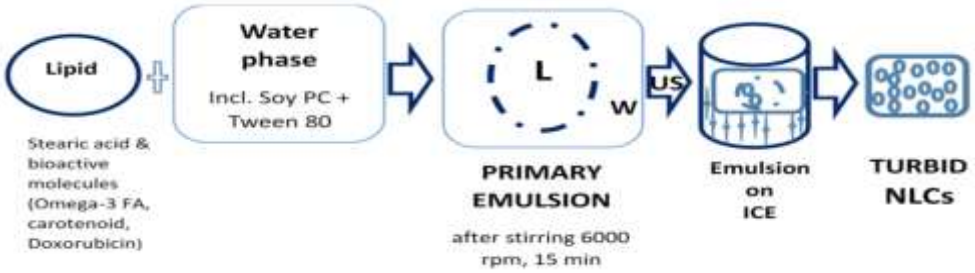

Fig 17: Image of Melt emulsification method.

6.4.5 Lipid emulsion/micro-emulsion template [107, 108]

The drug particles can also be mixed with a solvent that is partly water miscible to create an emulsion, which can then be diluted to create nanosuspensions. The creation of nanosuspensions may also be done using microemulsions as templates. Two immiscible liquids, such as oil and water, can be mixed together to create thermodynamically stable and isotropically transparent microemulsions in the presence of an interfacial coating of surfactant and cosurfactant. The medication may be put into the internal phase or disseminated in the prepared microemulsion. The drug nanosuspension will be produced when the microemulsion has been properly diluted. One of the documented uses of the microemulsion technique is the griseofulvin nanosuspension. Water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate were all employed in the production procedure. Water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate were all employed in the production procedure. The advantage of using lipid emulsions as templates for nanosuspension is that the nanosuspension's particle size can be adjusted. Additionally, scaling up the preparation is simple. The use of organic solvents, which may be hazardous, is the main disadvantage. Additionally, a significant number of stabilisers and surfactants must be utilised. The weakly water-soluble and poorly bioavailable anti-cancer medicine mitotane has been effectively manufactured into drug nanosuspensions utilising emulsion templates, with a notable improvement in drug dissolution rate (five-fold increase) noted when compared to the commercial version.

Advantages of micro-emulsion template

1) It is not essential to use specialist equipment.
2) Particle size may be readily changed by adjusting the emulsion droplet size.
3) If the formulation is adequately tuned, scaling up will be simple.
4) Production cost is low for preparation of nanosuspension as compared to other technique.

Disadvantages of micro-emulsion template

1) This approach cannot be used to create drugs that are poorly soluble in both aqueous and organic environments.
2) Diultrafiltration is required for the purification of the medication Nanosuspension, which may make the procedure expensive.
3) In comparison to the previous manufacturing procedures, a large amount of surfactant/stabilizer is required.

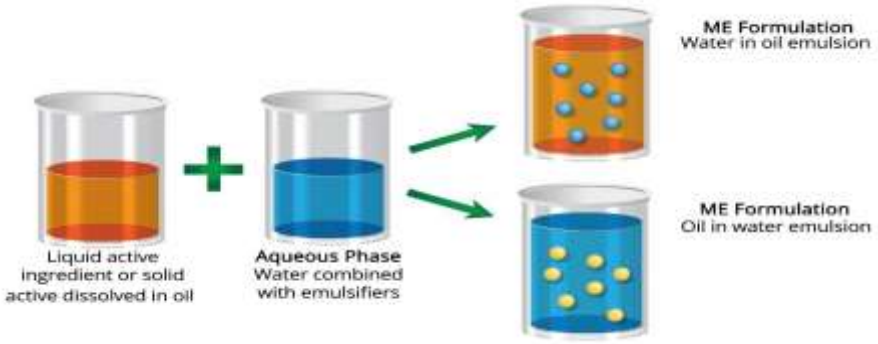

Fig 18: Image of Lipid emulsion/micro-emulsion template.

6.4.6 Nanojet technology [107]

Nanojet technology is a counter-current approach. A chamber is used in this technique to split the stream of suspension into two or more portions, and the particles colloid with each other under high pressure. The strong shear force created by the high-pressure technique can aid in particle size reduction. The microfluidizers M110L and M110S (microfluidics) are based on this principle. The main drawback of this

technology is that a significant number of microparticles might be generated when a large mass passes through the microfluidizer.

7. Production of nanosuspension on laboratory scale [49, 27, 108-111]

The cavitation forces produced in high pressure homogenizers, such as piston-gap homogenizers of the APV Gaulin type, are the disintegration principle for generating nanosuspensions. High-speed stirring is used to evenly distribute the medication powder in an aqueous surfactant solution. The resultant "macro"-suspension is put through three to ten up to twenty passes (= homogenization cycles) in a high pressure homogenizer that normally applies 1500 bar. In general, it is advised to begin with a powder that is as fine as possible; this entails a product that has been jet milled. The homogenizer's homogenization gap, which the suspension generally goes through, has a width of, say, about 25 m at 1500 bar. The suspension streams at a much faster rate because of the gap's narrowness, which raises the dynamic fluid pressure. The static pressure on the fluid simultaneously decreases below the temperature at which water reaches its boiling point. As a result of the high pressure, water begins to boil at room temperature. Gas bubbles are created, and as the fluid exits the homogenization gap, they collapse (=cavitate). The drug microparticles can be broken down into smaller drug nanoparticles by the cavitation forces.

The pressure and number of cycles used during this process, as well as the hardness of the medication itself, all determine the mean particle size in the nanoscale range that is achieved. For instance, a mean diameter of 330 nm for paclitaxel nanosuspension, 600 nm for clofazemine, and 540 nm for the medication RMKP22 have all been reported. Of course, the production parameters selected also affect their dimensions. In the case of budesonide, for instance, a pressure of 1500 bar and ten cycles results in particles with a mean PCS diameter of 511 nm, a cycle number increase to 15 results in a size reduction to 462 nm, and a pressure increase to 2500 bar and ten cycles results in particles with a diameter of 363 nm. In conclusion, by appropriately regulating the production parameters pressure and cycle number, a certain size may be generated in a regulated manner. There is a minimum size for each medication that can be obtained by applying a specific amount of pressure; this minimum size is influenced by both the drug's hardness and the power density of the homogenizer.

For example, the APV Micron LAB 40 (APV Deutschland GmbH, Lübeck, Germany) as well as various piston-gap homogenizers from Avestin (Aves tin Inc., Ottawa, Canada) and Stansted are homogenizers that may be utilised on a laboratory scale (Stansted Fluid Power Ltd., Stansted, UK). Because the LAB 40 offers a minimum batch volume of 20 ml and a maximum batch volume of 40 ml, even expensive medicinal ingredients may be processed affordably. Utilizing, for instance, the Avestin EmulsiFlex-B3 will enable the preparation of even smaller volumes (volume 3.5 ml). The preferred biopharmaceutical qualities and the type of the medicine (therapeutic field) determine the optimal nanoparticle size for nanosuspension.

A size of around 100-200 nm is ideal when a very quick disintegration is desired. The mean particle diameter may be set in the upper nanometer range, e.g., 800-1000 nm, when extended dissolution is needed (for example, mucoadhesive nanosuspension for treatment of Cryptosporidium infections). Larger nanosuspensions are preferable for intravenous injection to target MPS cells (to avoid complete dissolution of the particles before they reach the macrophages). Small nanosuspensions are better suitable for a quick medication disintegration in the circulation. It should be noted that there is no correlation between the size of the medication nanoparticles and the quality of the final output. For each therapeutic objective, a size that is specifically tailored is required.

Stanstead homogenizers typically treat suspensions with solid contents of 10 or 20%, while 40% suspensions have also been handled. The final use of the nanosuspension will determine the solid concentration that is selected. In order to further convert the nanosuspension into a dry product (for example, by granulating into tablets), 10% or even less solid content is required for intravenous injection; a greater solid content is preferred to remove less water.

8. Large-scale production of nanosuspension [48, 97, 112-114]

For a delivery system or dosage form to be introduced to the pharmaceutical market, it must be feasible and possible to produce it on a big scale. It is useless to have a very efficient distribution system if there is no way to manufacture it in sufficient quantities to meet market demand. Additionally, even in very wealthy nations, the production technology must be affordable to take into account the budgetary limitations of the health systems. Even with the current talks on the cost-to-patient benefit ratios, a technology that is practical but prohibitively expensive will not enter the market. In the middle of the 1980s, computations were done in the UK by multiplying a life quality metric

by the median patient survival period in years. The final sum was contrasted with the price per operation. This indicates that doing a highly expensive cardiac procedure was not seen as being cost-effective.

Fig 19: APV LAB 40 (APV Deutschland GmbH, Lubeck, Germany).

Compared to several inexpensive operations, such hip replacements, which produce a large number of survival years with a good quality of life, replacement for one patient results in a restricted quality of life. Consequently, the cost of a technology is becoming a greater and more crucial component.

When considering polymeric drug nanoparticles, the significance of having a large scale production facility becomes clear. Despite the fact that this delivery method has been the subject of extensive study for more than 30 years, it is not now available on the market. There is just one product, Abdoscan by Nycomed, although it is a diagnostic agent for single administration rather than a chronic illness therapy solution (meaning a product with less problems regarding regulatory acceptance). There are numerous various explanations for the dearth of goods on the market, depending on the type of nanoparticles.

However, from our perspective, a fundamental cause is the absence of a large-scale production technique that would result in a good enough product for the regulatory bodies. A crucial aspect is that simply having a production line that can produce in vast quantities is completely insufficient. This manufacturing line must be appropriate for qualification and validation in order to be accepted by the regulatory authorities. The technology must also be reasonably priced. Meeting all these parameters for the manufacturing of polymeric nanoparticles is still a challenge. Unlike this medicine, nanoparticles are easily generated on a big scale utilising the high-pressure homogenization process, which is currently used in several sectors for large-scale manufacturing.

There are numerous high pressure homogenizers with capacities ranging from a few hundred to a few thousand liters per hour. The high pressure homogenization technique is widely established in a variety of applications, from the preparation of food to lubricants. Pharmaceutics uses high pressure homogenization to create emulsions for parenteral nutrition, which implies there are production lines accessible for parenteral goods.

The macro suspension must pass through a high pressure homogenizer between three and five/ten or a maximum of 20 times in order to produce a nanosuspension. To create the result in a continuous manner, three homogenizers can be connected in series as opposed to, say, putting the mixture through one homogenizer three times. Because the homogenizers are low-cost and readily available off-the-shelf equipment, using three of them is feasible. The Rannie, which has a 1000-1 capacity and a maximum pressure of 1500 bar, is an appropriate homogenizer. Where more cycles are needed, connecting homogenizers in series is less cost-effective. Applying a discontinuous mode of one homogenizer, for instance, would be a low-cost option with five cycles and a relatively modest batch size of, say, 1000. The suspension will be fed through the homogenizer and into the product container from the feeding container, then back again, and so on, for a total of five passes to be made within five hours of production If 10 cycles are necessary, two homogenizers might be placed in between the containers to maintain a 5 h production time.

Pearl milling needs milling durations ranging from hours to a few days to produce drug nanoparticles. Milling over a period of many days carries the danger of microbiological issues, particularly when done at ambient temperature or with dispersion media that feeds bacteria. As a result, generating drug nanoparticles by high pressure homogenization has a fundamental benefit of having production timeframes that are typically a few hours. High

pressure homogenization furthermore has a sterilising effect. It is a method used, for instance, to break bacteria-containing cells, improving the quality of microbiological products.

The contamination of the product caused by erosion from the production equipment is another crucial factor. Pearl factories have the danger of having debris from the pearls eroding away and contaminating their finished product. Eroded particle material might be problematic, even for oral delivery. It is possible for pearls to produce microparticles, which may interact with the M cells in Peyer's patches and have unclear effects on the immune system. It is also thought that one method for oral vaccination involves particle absorption by the M cells, therefore disruptions of the immune system caused by ongoing administration of non-biodegradable microparticles cannot be completely ruled out. Products made by high pressure homogenization are free of this contamination. Metal ions ejecting from the homogenizer wall might potentially contaminate the nanosuspensions. The metal contamination in nanosuspensions produced under difficult circumstances—20 cycles at a maximum pressure of 1500 bar—was examined. Iron was examined in the nanosuspensions since it is the most prevalent ion in steel; it was discovered to be below 1 ppm, which is an uncritical threshold.

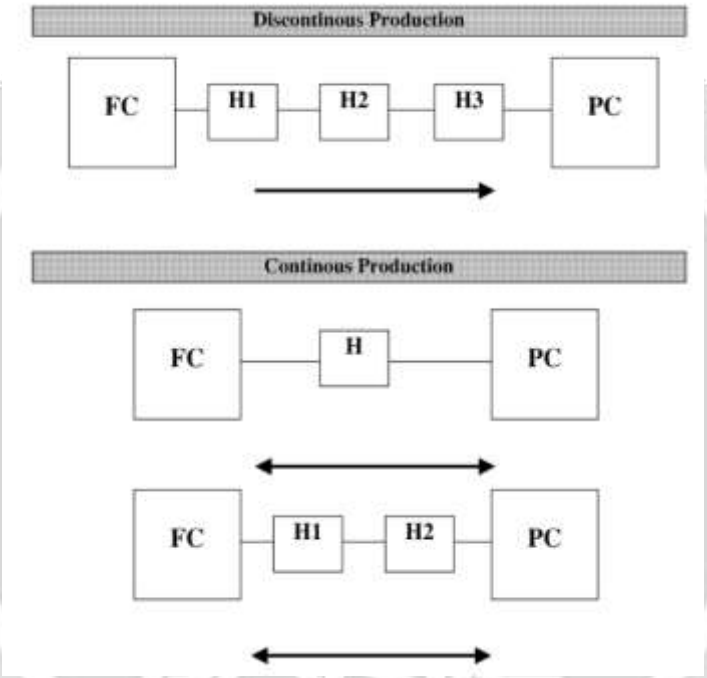

Fig 20: Image of Production-line diagram Production of nanosuspensions utilising three passes (cycles) by employing three homogenizers (H) in succession, using five to ten cycles by repeatedly passing the product through one or two homogenizers (5discontinous production, top) (5discontinous production, middle and lower; FC, feeding container; PC, product container).

9. Formulation consideration

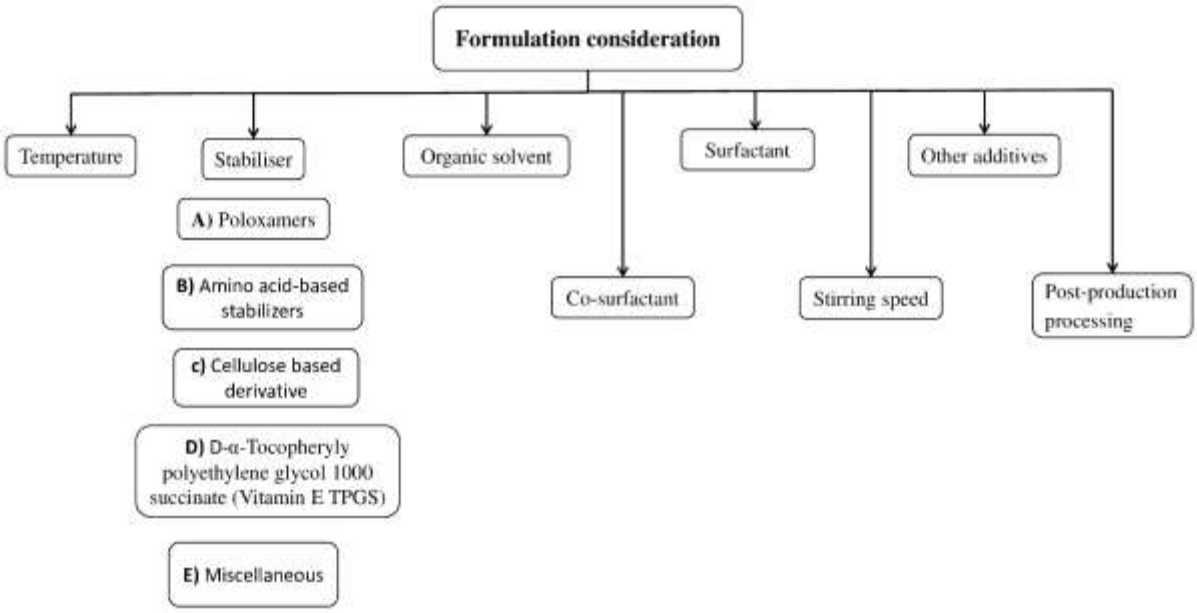

Fig 21: Types of formulation consideration.

9.1 Temperature [111, 115]

While creating the nanosuspension, it is crucial to maintain the ideal temperature. In the emulsion approach, when the drug-containing organic solution is introduced to the aqueous surfactant solution, homogenization takes place at a lower temperature. Given that organic solvents are used in the formulation and that a higher temperature can hasten the elimination of organic solvent, maintaining a low temperature is a very critical safety precaution to take. The creation of spherical and homogenous nanoparticles is encouraged if a lower temperature is maintained during formulation because the solvent diffuses out of the solution slowly.

9.2 Stabilizer [111, 115, 116]

The nanosuspension formulation process depends heavily on the stabiliser. In order to create a stable formulation, the stabiliser must be able to thoroughly wet the nanoparticles and provide steric or ionic barriers to prevent the Ostwald's ripening and agglomeration of nanosuspensions. The ratio of medication to stabiliser in various formulation procedures ranges from 1:20 to 20:1, and a combination of stabilisers may be necessary. The kind and quantity of stabiliser significantly affect the nanosuspension's physical stability and in vivo behavior. Investigations into particular nanosuspension are necessary. The most extensively researched stabilisers include povidones, cellulosic, polysorbates, poloxamers, and lecithin. Other additives, such as cosurfactants, buffers, salts, and polyols are added to improve the formulation of nanosuspensions. However, while selecting the additives, the medication formulation's method of administration or the characteristics of the drug particles should be taken into account.

According to published research, APIs with high log P and enthalpy values have a better chance of forming stable nanosuspensions through both steric and electrostatic stabilisation. Furthermore, it did not appear that physical characteristics such molecular weight had a direct bearing on the particle size or stabilisation stage. The strength of attraction between neighboring particles in the system that are similarly charged is determined by the zeta potential measured at the shear plane. Although the size of the zeta potential normally indicates the stability of the nanosuspensions in terms of their physical stability, this may not be the case for stability attained by electrostatic stabilisation. This is because the dissociation of charged functional groups on the particle surface, which is influenced by both the medium's pH and the drug's pKa, also accounts for the electrical properties at the interface. Surface free energy and functional groups are particularly important in the dynamic stage of nanosuspension production, which is a complicated interplay involving many different elements. The durability of the nanosuspensions as well as the effectiveness of the chosen methodology may be determined by the faster surface adsorption rate of stabiliser throughout various preparation procedures as opposed to newly generated surface.

The solubility and therapeutic efficacy of nanosuspension can be dramatically altered by the polymorphic and amorphous-crystalline transition. This is due to the fact that electrical properties at the interface are also caused by the dissociation of Solid state stability involving API's crystal defects during the milling process. Powder X-ray diffractometer (XRD) research supported by other physical characterization methods can be used to compare the percentage of crystalline/amorphous content with physical mixtures. Small angle X-ray scattering, as opposed to X-ray diffractography, may provide details on the size, shape, orientation, and crystallinity and amorphinity of a range of polymers, proteins, and nanomaterial bioconjugate systems in solution. Modulated differential scanning calorimetry is commonly used to assess the thermal properties of the air/freeze dried nanosuspension powder. To generate long-circulating properties and accomplish passive drug targeting through the increased permeability and retention (EPR) effect, maintaining in vivo stability is essential. Since aqueous media is routinely used to create nanosuspensions, problems with oxidation and hydrolysis must be addressed. Thus, a stabilizer's crucial role in preventing aggregation or agglomeration brought on by the nanoparticles' high surface energy. Various types of particle size analyzers may be used to investigate any variations in particle size distribution and polydispersity index at various stages of nanosuspension, such as during manufacture, storage, and stability conditions.

9.2.1 Poloxamers [117]

Poloxamers The FDA has approved these synthetic polymers for topical, parenteral, and oral pharmaceutical uses. They are generally recognised as safe (GRAS). Poloxamer 188 and Poloxamer 407 are the Poloxamers used in nanosuspension the most commonly. Molecular weight, morphology, functional groups, and the hydrophilic-lipophilic ratio are the main variables that affect the stability and development of nanosuspension crystals.

9.2.2 Amino acid-based stabilizers [115, 117]

It has been proven that leucine copolymers may successfully create stable drug nanocrystals in an aqueous media. As a stabilising ingredient for sterile, steam heat sterilizable parenteral nanosuspensions, lecithin is chosen. As little as 0.003% up to 5% in nanosuspension, albumin has been used as a surface stabilisation and drug targeting agent. Arginine, proline, and transferrin were additional pharmaceutically approved amino acid co-polymers employed to increase the physical stability of nanocrystals.

9.2.3 Cellulose based derivative [117]

As stabilising agents in nanosuspensions, HPMC, hydroxypropyl cellulose (HPC), and hydroxyethyl cellulose (HEC) are frequently utilised. These polymers' ability to provide steric stabilisation is based on hydrophobic groups that have been adsorbed to their surfaces.

9.2.4 D-α-Tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS) [111, 118]

An esterified, water-soluble vitamin E (tocopherol) derivative known as vitamin E polyethylene glycol succinate is employed as a stabilising and solubilizing ingredient in several nanosuspension formulations. For oral, ophthalmic, and parenteral uses, it is regarded as the most effective excipient due to its high physical stability and low toxicological profile.

9.2.5 Miscellaneous [43, 118]

The polyvinyl caprolactam-polyvinyl acetate-PEG copolymer used in Soluplus® is a brand-new excipient created by BASF Industries. Many nanosuspension with improved stability, higher dissolving rate, and bioavailability have employed it as a stabiliser. The rate of dissolution and bioavailability of nanosuspensions were shown to be greatly increased by water-soluble polymers utilised as stabilisers, such as polyvinyl alcohol (PVA), polyvinyl pyrrolidone, and PEGylated chitosan. Beclomethasone dipropionate was given a functionalized surface coating using hydrophobic, a protein-based surfactant. It is ideal for many drug delivery applications due to its adaptability for surface modification through genetic engineering.

9.3 Organic solvent [119, 120]

Sometimes organic solvents are necessary for the formation of nanosuspensions. Therefore, while choosing the organic solvent, possible toxicity and how simple it is to remove them from the formulation should be carefully taken into account. In general, it is thought that pharmaceutically acceptable and less dangerous solvents include

those that are water-miscible, such ethanol and isopropanol, as well as those that are partially water-miscible, including ethyl format, propylene carbonate, triacetin, butyl lactate, and benzyl alcohol. In the formulation process, such solvents are preferred to the traditional dangerous halogenated solvents, such as chloroform and dichloromethane. Furthermore, when producing nanosuspensions utilising a microemulsion as a template, partly water-miscible organic solvents can be employed as the internal phase of the microemulsion.

9.4 Co-surfactant [72]

When analysing nanosuspensions utilising smaller size emulsions, co-surfactant selection is crucial. Since co-surfactants can significantly alter stage, their direct impact on internal stage uptake for chosen scaled-down scale emulsion procedures and drug stacking should be researched. When creating Nanosuspensions utilising micro emulsions, the co-surfactant selection is crucial. The impact of cosurfactants on internal phase uptake and drug loading for a particular micro emulsion composition should be examined since they have a significant impact on phase behavior. Although bile salts and dipotassium glycerrhizinate are mentioned in the literature as cosurfactants, other solubilizers, including Transcutol, glycofurol, ethanol, and isopropanol, can be employed in the creation of microemulsions without risk.

9.5 Surfactant [120]

By lowering the interfacial tension, surfactants are added to enhance the dispersion. They also function as wetting or deflocculating agents, such as the commonly used surfactants Tweens and Spans.

9.6 Other additives [120]

Depending on the method of administration or the characteristics of the drug moiety, nanosuspensions may contain additives such buffers, salts, polyols, osmogent, and cryoprotectants.

9.7 Post-production processing [120, 121]

Nanosuspensions require post-production processing when the drug candidate is extremely vulnerable to hydrolytic cleavage or chemical degradation. Processing can be necessary if even the best stabiliser is unable to keep the nanosuspension stable for an extended period of time or if the targeted route has acceptance requirements. Taking into account these factors, methods like lyophilization or spray drying may be used to create a dry powder of medication particles that are nanoscale in size. In these unit activities, a rational choice must be made while taking the drug's qualities and the economy into account. In general, spray drying is less expensive and more practical than lyophilization. It is important to take into account how postproduction processing affects the moisture content of dried nanosized drugs and the particle size of the nanosuspension.

9.8 Stirring speed [119]

It is simple to overlook the stirring speed as a crucial element in the creation of nanosuspension. Smaller nanoparticle suspensions may be produced via high-pressure homogenization (HPH) or high-shear homogenization (HSH) of nanosuspensions. The HSH method can readily produce drug particles in the nanoscale by speeding up the stirring, while the HPH process can do so by increasing the number of cycles. However, with the instruments running at a fast speed, a significant amount of foam in the suspension will be produced. As a result, size reduction and the production of homogenous nanoparticles may be less effective. As a result, it's crucial that the instruments are operated at the required speed and cycle number.

10. The common stability issues of nanosuspensions

10.1 Aggregation

Despite the formulations for nanosuspensions having various benefits, the nanosuspensions are not permanently stabilised by improper stabilisers, and aggregation may happen during storage or the solidification process. Due to the Ostwald ripening phenomena, the improper stabilisers caused smaller particles to aggregate in the nanosuspensions. Ostwald ripening is a phenomena in which tiny particles re-dissolve while coarse particles increase. In other words, mass transfer from the fines to the coarse particles happened because nanocrystals of smaller sizes are more soluble than those of larger sizes [108, 121, 122].

The medications should be poorly soluble in order to prevent aggregation and Ostwald ripening, which would result in minimal changes in the dissolved concentration throughout the manufacture of nanosuspensions. Additionally, the generated nanosuspensions' particle sizes should be somewhat uniform to prevent significant discrepancies in the saturation solubility of variously sized crystals. The nanosuspension, on the other hand, is a thermodynamically unstable colloid disperser system. As a result, aggregation is a fundamental characteristic of nanosuspensions and is due to both the Ostwald ripening and the propensity of nanoscale systems to lower Gibbs free energy [122, 123].

Therefore, one of the key tasks during the creation of nanosuspensions is to figure out how to restrict or limit this aggregation. For the creation of stable nanosuspensions, a suitable stabiliser is required. The likelihood of an individual stabiliser interacting with the medicinal ingredient affects how effective it is. The two most popular stabilising agents utilised to create stable nanosuspensions are steric and ionic stabilization [123].

The aggregation might have happened either during the cooking procedure or the shelf-time. When producing nanosuspensions via a top-down method, as surface area increased, drug particles of nanoscale began to aggregate owing to the thermodynamic effect, ultimately decreasing the process' efficiency. Because a stabiliser is required to coat the surface of nanoparticles during milling or high-pressure homogenising, its application is crucial. Aggregation becomes a more significant stability concern during storage. The selection of the proper stabilisers and concentration may be the crucial stability criteria. Particles from nanosuspensions may have the amphiphilic polymer, such as TPGS, adsorbed onto their surface. Additionally, the adsorbed chain molecules on the surface are constantly moving due to thermal advection, creating a dynamically rough surface that prevents coalescence by the action of a repulsive entropic force. For instance, during the stability research at the 6 week time point, the NVS-102 nanosuspensions' levels of d-alpha tocopherol polyethylene glycol 1000 succinate (TPGS 1000) at a 4:1 (drug: TPGS 1000) ratio had demonstrated a considerable increase of nanocrystals. However, the ratios of 2:1 and 1:1 (drug: TPGS 1000) produced nanosuspensions that were more stable in terms of particle size and showed no aggregation or crystal formation during storage. Furthermore, TPGS 1000 and hydroxypropyl methylcellulose (HPMC) 3 cps had synergistic stability benefits for preventing aggregation. The frequently used suspending agent, HPMC, which is utilised in suspension formulation, may be able to decrease the sedimentation rate and raise the viscosity of the nanosuspensions. Additionally, it was also capable of forming stereospecific blockades between nanosuspension particles, which prevented the particles from touching one another and causing aggregation [121-124].

10.2 Sedimentation [122-125]

Colloidal dispersions included nanosuspensions. Colloidal dispersions fall between actual solutions and coarse dispersions in size when compared to true solutions, while molecular dispersions are homogenous. Sedimentation is the most extreme manifestation of the unstable nanosuspension phenomenon. Typically, the first stage of instability is the aggregation and the Ostwald ripening. From molecular dispersions to colloids or from colloids to coarse dispersions, the transfer of size ranges happens relatively gradually. However, sedimentation will unavoidably occur if the drug particle's gravity is larger than the buoyancy force that the system's provisioned for. This procedure is both unrepeatable and irreversible. The main factor in creating nanosuspensions is therefore how to anticipate and avoid sedimentation. For instance, PVA stabilised nanosuspensions of ciclosporin A (CsA) did not exhibit creaming or sedimentation processes and produced the tiniest particles, which were around 530 nm in size.

In addition to the stabilisers' propensity to cause the sedimentation of nanosuspensions, other variables may also contribute to this instability. In microfluidic reactors, acetaminophen nanosuspension was created via nanoprecipitation. Surfactant concentration, solvent and anti-solvent flow rate, and solvent temperature were employed as input factors. The time it took for nanosuspensions to sediment was taken into consideration as an output variable. It was discovered that temperature and the flow rate of the anti-solvent have a direct relationship with the time of sedimentation whereas the flow rate of the solvent typically has a reverse relationship with the time of sedimentation.

10.3 Crystalline transformation [123-125]

The usual method for further enhancing the physical and chemical stability of the nanosuspensions is the solidification process, such as freeze-drying and spray drying. However, the formation of the amorphous, noncrystalline forms only requires a little amount of energy during the solidification process. In other words, the amorphous form's production uses a lot less energy than crystallisation does. Theoretically, an optimal way to further increase the dissolving rate is to have completely or partially amorphous states of insoluble medicines in nanocrystals. In contrast to their crystalline counterparts, nanocrystal molecules in the amorphous form are

thermodynamically unstable. A crystalline nanosuspension medication is therefore more stable and frequently better. And to make matters worse, there was a lack of effective regulating techniques for this shift. As a result, after the production process produces amorphous material, there is a possibility that it will crystallise during release or storage, making crystalline transition an issue that must be dealt with during the storage stage of nanosuspensions.

The solubility will be produced by the crystalline transition, changing the therapeutic effects. The possibility exists that an API's crystalline transformation between crystallise and amorphism during storage for a compound of nanosuspensions produced with polymorphism. Along with losing advantageous qualities (high solubility and high dissolving rate), the formulation change also brought up an instability issue.

10.4 The plasma stability [62, 59, 126-128]

In addition to oral dose forms, intravenous distribution is another essential method for administering nanosuspensions that include water-insoluble chemicals. The produced nanosuspensions' compatibility with plasma is therefore a crucial concern. In order to achieve passive drug targeting to disease sites with leaky vasculature via the enhanced permeation and retention (EPR) effect, it is evident that a crucial property of nanosuspensions formulations is their capacity to alter pharmacokinetics and, in particular, to demonstrate long-circulating properties. The nanosuspensions must thus exhibit good physical stability features after intravenous injection, preserving appropriate structural integrity, offering a longer drug half-life, and enhancing drug exposure (AUC) in comparison to free drug.

We believe that every factor, including but not limited to particle size distribution, surface charge, morphology, and surface hydrophilism/hydrophobicity, as well as the infusing rate and concentration, is a potential cause of instability of the nanosuspensions because they all significantly influence their stability both in vitro and in vivo. The surface charge and surface hydrophilism/hydrophobism may be the primary influencing factor for producing the instability in plasma among all other possible causes. The environment of the nanosuspensions changed dramatically when they were pumped into the plasma, including pH, ionic strength, etc. This might have affected their surface charge and zeta potential and caused them to aggregate. However, despite our plans, there hasn't yet been a unique study published that specifically addresses the variables that affect in vivo stability.

10.5 The chemical stability [127-129]

In addition to the nanosuspensions' physical durability, as was already noted, the pharmaceutical industry places a lot of emphasis on their chemical stability when developing drug delivery systems. There were a few processes that were run in non-aqueous mediums, but generally the nanosuspensions were created in a dispersion medium of water or water combination settings. Therefore, while producing nanosuspensions, chemical stability issues including oxidation and hydrolysis are a major concern. And this is the lack of chemically stable nanosuspensions for drugs. The final solid and concentrated condition shielded the medication from the risk of photoallergic, hydrolyses, and oxidation, but it's also a possible method for increasing the chemical stability for chemically labile pharmaceuticals. But for hydrolyzes labile chemicals, the question of how to make nanosuspensions that are chemically stable is difficult and problematic.

According to the paper, quercetin molecules' chemical and photo-stability in nanosuspensions was significantly improved over that of the solution kept under the same circumstances. Along with maintaining activity, the greater chemical stability may also help quercetin's toxicity to be lessened. The following explanations may help to explain the increased stability. The stabiliser molecules coating the nanocrystals' surface might protect the interior compound from oxygen and light. Due to the nanosuspensions' limited access to water and light at the stabilizer-uncovered particle surface, a deteriorated outer monolayer of molecules would form to protect the drug nanoparticles' inner portion (similar to oxidised layer on top of aluminium). Only a small number of molecules deteriorated even in this outer layer because of the stabilising layer's protection. In order to increase the stability of chemically labile medications like quercetin and curcumin, nanosuspensions technology may be applied.

Omeprazole is a proton pump inhibitor that degrades rapidly in aqueous conditions due to its low solubility and chemical lability. Omeprazole was created by Moschwitzer et al. as nanosuspensions. The HPLC analysis demonstrated that the nanosuspensions produced by high pressure homogenization (HPH) were significantly more chemically stable than an aqueous solution. When the nanosuspension was stored at 0° C, no colour change or drug loss was seen even one month following synthesis.

11. Characterization of nanosuspensions

The following are the important characterization factors for nanosuspensions.

11.1 Color, Odor, Taste Evaluations [130]

These characteristics have special importance in formulations intended for oral administration. A change in crystal behavior and particle size that affects dissolving can change the flavor. A changed colour, smell, or taste might be a sign of chemical instability.

11.2 Mean particle size and particle size distribution [129, 131-133]

The saturation solubility, dissolving velocity, physical stability, and even biological performance of nanosuspensions are all governed by the mean particle size and the breadth of the particle size distribution, which are crucial Characterisation characteristics. According to Muller & Peters (1998), there is a significant relationship between the drug's changing particle size and its saturation solubility and dissolving velocity.

The mean particle diameter of nanosuspensions may be quickly and precisely determined using photon correlation spectroscopy (PCS). Additionally, PCS may be used to calculate the polydispersity index, or PI, which measures the breadth of the particle size distribution. For long-term stability of nanosuspensions, the PI, a crucial parameter that controls the physical stability of nanosuspensions, should be as low as feasible. In contrast to a PI number larger than 0.5, which suggests a very broad distribution, a PI value of 0.1-0.25 implies a relatively tight size distribution.

Such a high PI number cannot possibly be explained by a logarithmic normal distribution. Although PCS is a flexible method, its narrow measurement range (3 nm to 3 m) makes it challenging to assess the likelihood that microparticulate medications (those with a particle size bigger than 3 m) would contaminate the nanosuspension. Laser diffractometry (LD) analysis of nanosuspensions should thus be performed in addition to PCS analysis in order to detect and quantify any drug microparticles that may have been created during the manufacturing process. Laser diffractometry produces a volume size distribution and may be used to measure particles with sizes ranging from 0.05 to 80 m, and in certain equipment, up to 2000 m. The diameter 50% LD (50) and diameter 99% LD (99) values, which denote that 50 or 99% of the particles are smaller than the stated size, are determined as part of the usual LD Characterisation. For nanosuspensions intended for parenteral and pulmonary distribution, the LD analysis becomes essential. Since the smallest blood capillary is 5–6 m in diameter, there may be a chance of capillary obstruction or emboli production even if the nanosuspension only comprises a tiny number of larger particles. It should be noted that LD data are volume based, but PCS mean diameter is the size weighted by light intensity, hence the particle size data of a nanosuspension acquired by LD and PCS analysis are not similar. The 50 or 99% diameter from the LD study and the PCS mean diameter are likely to be different, with LD data often showing greater values. Deionized water can be used to appropriately dilute the nanosuspensions prior to PCS or LD analysis.

Along with PCS and LD measurement, particle size analysis using the Coulter counter technique is crucial for nanosuspensions meant for intravenous delivery. The Coulter counter is a more effective and suitable technology than LD analysis for assessing the contamination of nanosuspensions by microparticulate medicines since it provides the absolute number of particles per volume unit for the various size classes.

11.3 Crystalline state and particle morphology [133, 134]

Understanding the polymorphism or morphological changes that a medicine may go through when subjected to nanosizing is made easier by combining an evaluation of the crystalline state and particle morphology. Additionally, it's conceivable that drug particles in an amorphous state will form during the preparation of nanosuspensions. As a result, it is crucial to look into how many amorphous drug nanoparticles are created during the creation of nanosuspensions. Differential scanning calorimetry can be used in addition to X-ray diffraction analysis to assess the changes in the physical state of the drug particles and the amount of the amorphous fraction. Scanning electron microscopy is recommended to provide a more accurate picture of particle morphology.

11.4 Particle charge (zeta potential)

It is crucial to determine a nanosuspension's zeta potential because it provides insight into the nanosuspension's physical stability. A nanosuspension's zeta potential is controlled by both the stabiliser and the medication. A minimum zeta potential of 30 mV is needed for an electrostatically stabilised nanosuspension in order to achieve satisfactory stability, whereas a minimum zeta potential of 20 mV is preferred for a combined electrostatic and steric

stabilisation. Drug nanoparticles can avoid precipitation and potentially severe aggregation thanks to the electrostatic repulsion produced by charges on particle surfaces [103, 119, 134].

The electrical potential between the Stern layer and the diffusion layer of ions with opposing charges is known as the zeta potential. The zeta potential must be carefully maintained throughout the nanosuspension's manufacturing and storage processes. The zeta potential may be determined with a zetasizer. To provide an appropriate concentration in which the electrophoretic cell may be dipped, the medication is dissolved in Milli-Q water. The original dispersion media, physiological salt solutions, or buffers with various molarities are often used for zeta potential measurements. The procedure can also be carried out by diluted the medicine in water. A different zeta potential from the real value may result from such dilution, which might also slightly change the surface charge [134].

The zeta potential may also be used to determine how strongly stabiliser molecules attach to particle surfaces and how much they adsorb there. Electroacoustic or laser light scattering techniques can be used to detect the zeta potential. These methods measured the mobility of the particles electrophoretically in an electric field. By allowing measurements in diluted dispersions, the electroacoustic approach offers an advantage over laser light diffraction [135].

11.5 Saturation solubility and dissolution velocity

To examine changes in the in vivo performances of medications, such as bioavailability, plasma peak, and blood profile, the saturation solubility and dissolution velocity are two crucial measures. It is important to look at a nanosuspension's saturation solubility since it is widely known that nanosuspensions are frequently utilised to increase the drug's saturation solubility [18]. Another crucial factor for a nanosuspension that demonstrates its advantages over traditional formulations is the dissolving velocity. As a result, it's important to evaluate the drug nanosuspensions' saturation solubility and dissolution rate under various circumstances, such as in various physiological buffers and at various temperatures [24, 135].

11.6 The density [136]

The formulation's actual gravity or density is a crucial parameter. The absence of density suggests that there is air trapped inside the formulation structure. To measure density at a certain temperature, a well-mixed, homogeneous formulation should be used; this type of measurement is facilitated by the precision hydrometer.

11.7 The value for pH [136]

The pH value for aqueous formulations must be measured at a certain temperature and after equilibrium settling in order to reduce pH drift and suspended particle surface coating with electrodes. The exterior phase of the formulation should be free from electrolyte to establish pH stability.

11.8 The size of droplet [137]

For micro-sized emulsion carriers, droplet size distribution is also calculated using microscopic or light scattering methods. a neon laser with a wavelength of 632 nm for a dynamic light dispersion spectrophotometer.

11.9 Nanosuspension stability [136, 137]

Drug crystals clump together as a result of the stimulated nanosized particles brought on by the higher surface energy. The main goal of the stabiliser is to fully wet the drug particles in order to prevent Ostwald ripening and/or agglomeration in nanosuspension, which creates a chemically stable preparation by acting as a steric and/or ionic barrier. For nanosuspensions, stabilisers such cellulosic, polysorbates, and lecithin are frequently utilised. Lecithin may furthermore be preferred in the creation of parenteral nanosuspension.

11.10 In vivo biological efficiency [12, 137]

The study must include an in vitro/in vivo correlation as well as monitoring the drug's in vivo output regardless of the route and therefore the delivery strategy employed. It is crucially important when using an intravenously administered nanosuspension. Since the distribution of the organ and subsequent drug surface characteristics like surface hydrophobicity and plasma protein binding determine how the drug behaves in vivo. Effective methods must thus be employed in order to measure the surface characteristics and protein interactions to encourage an understanding of in vivo behavior.

12 Dosage form of nanosuspension DDS [137]

Poorly soluble medications can be administered both in liquid dose form and solid dosage form. Nanosuspension DDS has so far been produced in a number of liquid or solid (powder, tablet, pellet, pill, and film) dosage forms.

12.1 Liquid dosage form [136, 138]

The drug nanoparticles are disseminated in the appropriate solvent medium in the liquid nanosuspension. Liquid dosage forms are superior to other dosage forms in that they are easier to split into smaller doses, absorb quicker, and have a better drug bioavailability. For oral delivery, liquid nanosuspensions of the poorly soluble medicines can be made. Aripiprazole, febuxostat, paclitaxel, myricetin, pranlukast, herpetrione, itraconazole, probucol, and revaprazan hydrochloride are some recent examples.

12.2 Powder dosage form [136-138]

The liquid nanosuspension of prospective drug candidates can be converted into a powder form as alternative dose form for nanosuspension DDS. Prior to usage, the dry powder form is readily redispersed in water or another liquid medium due to its long-term stability. In addition, dry medication powders dissolve quickly and are simple to redisperse into nanosuspensions. According to the in vivo pharmacokinetic study, the redispersed nanosuspensions show a high oral bioavailability.

Many poorly soluble medications, including scutellarin, naproxen, Novartis Compound A, itraconazole, and bexarotene, have recently been administered using the powder dosing technique. Yang et al. are one example. (2014) used the freeze-drying technique to convert an aglycone scutellarein nanosuspension into a dry powder. The dry powder dosage's rate of dissolution increased as compared to coarse medication. Additionally, it was simple to wet and re-disperse the medication powder dose into a liquid medium. The dry powder easily dissolved and redispersed into a nanosuspension and exhibited a high dissolving rate. Its BCS class IV glycoside scutellarin is an active and quickly absorbed oral precursor nanosuspension DDS, according to an in vivo pharmacokinetic analysis of the redispersed dose in rats.

12.3 Pellet dosage form [139-141]

Pellet, another solid dose form, has a number of benefits including little irritation of the gastrointestinal tract and reduced susceptibility to the impact of stomach emptying. Fluid-bed coating technique enables the direct conversion of liquid nanosuspensions into pellet dose. The drug-loaded pellets retained the drug nanocrystals' original size and size distribution even after being redispersed in water. In addition, compared to the coarse pharmaceuticals, the drug-loaded pellets also demonstrated a quicker rate of disintegration. The drug-loaded pellets were influenced by a variety of factors, including the type of binder. Fluid-bed coating method was used to create the liquid hydrocortisone acetate nanosuspension, which was subsequently transformed into pellets with sugar beads serving as the pellet cores. Various binder solutions were employed throughout the production, including chitosan chloride, polyvinyl alcohol, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Except for polyvinylpyrrolidone, all of the tested binders were compatible with the nanosuspension. Furthermore, the binder types undoubtedly had an impact on the zeta potential, stability, and dissolution characteristics of the final pellet doses.

Using an extrusion-spheronization process, dry powder dosage may also be converted to pellet dosage. Excipients are initially combined with drug nanoparticle powder in the multi-step extrusion-spheronization preparation process, which is then followed by wet granulation, extrusion, spheronization, and drying. The work of Mauludin et al. provided a typical example. They created a liquid ibuprofen nanosuspension in their research, which was later dried into powder. The extrusion-spheronization procedure was then used to turn the dry ibuprofen nanosuspension powder into pellets. The Ibuprofen nanocrystal in the pellets shown good behaviors similar to the dose of powder and could be totally redispersed in water.

12.4 Tablet dosage form

One of the most widely used dose forms today, compressed tablets make up over one-third of all prescriptions filled. The tablet dosage form enjoys great popularity not only due to the ease with which a precise drug dosage and uniform content can be delivered to a particular site, but also because it can be used for administration methods other than oral administration such as sublingual, buccal, rectal, or intravaginal [47]. There are a few procedures involved in creating the dosage form for tablets.

Drug nanoparticle powder was created by first solidifying a liquid nanosuspension of drug particles, which was then combined with excipients. The resultant mixture can be mechanically pressed into tablet dosage form [30]. Alternatively, you can combine the medication with water-soluble excipients in a PVC blister and freeze it to create tablet dosage form. Tablets for medications with low solubility have garnered a lot of interest. Itraconazole pills were made by Sun et al. (2015), and then the formulation was improved. Regarding medication content and in vitro dissolving characteristics, the tablets were stable. The oral absorption of the itraconazole pills was equivalent to that of the leading market product, according to in vivo data. Patel et al. (2014b) created tablets with telmisartan within that were nanosized [99,105]. According to the in vitro drug-release investigation, the tablets' dissolving rate was significantly higher than that of commercially available telmisartan tablets. An in vivo pharmacokinetic investigation revealed that the oral bioavailability of the nanosized telmisartan-loaded tablets was 1.5 times greater than that of the marked telmisartan tablets. Additionally, it was claimed that tablets containing nanosized silybin, tadalafil, and fenofibrate nanoparticles had enhanced bioavailability. These studies' findings imply that the tablet is a superior dosage form for the oral delivery of medications with limited water solubility [131].

It is widely known that adding polymers like Poly (DL-lactide-co-glycolide) and complexing agents like cyclodextrin can improve the biopharmaceutical performance of medications that are not readily soluble in the body. It has been proven that the main determinants of granule physicochemical parameters, including redispersibility and particle size distribution, are concentration of nanosuspension, spraying rate, and atomization air pressures.

12.5 Capsule dosage form

The drug nanoparticles are inserted in the hollow hard capsule or sealed in the elastic soft capsule for the capsule dose form. The solid dose form in capsules has the benefit of being odourless and having high stability [141].

Dry drug nanoparticle powder can be put inside a capsule to create a dose of drug nanoparticles. According to Bose et al. (2012), wet milling was initially used to create the nanosuspension before it was turned into powder using the fluid-bed spray granulation method. This process was then used to prepare capsules for oral administration [41]. A firm gelatin capsule was then filled with the resulting powder. Itraconazole powder dose was manufactured as dried crystalline itraconazole powder, and utilising a capsule filler, the powder was then encapsulated in firm gelatin capsules. The drug nanocrystal-laden capsules showed a greater dissolving rate and a significantly increased in vivo bioavailability when compared to micronized drug loaded and commercial capsules [142].

By inserting the pellets containing the drug nanoparticle into a capsule, a different method of preparing capsule dose with the drug nanoparticle may be achieved. Mitri et al. (2011b) initially created a liquid lutein nanosuspension using high-pressure homogenization, and the nanosuspension was then transformed into pellets through the use of the extrusion-spheronization procedure. The gelatin capsules were then filled with the pellets for oral delivery [142, 143]. The lutein medication nanoparticle-loaded manufactured capsules display an improved in vitro release (usually 3–4 factor).

12.6 Film dosage form

Oral films, also known as orodispersible films, offer significant benefits over other oral dosage forms because they quickly dissolve in the mouth, quickly traverse the oral mucosa, and skip hepatic metabolism, increasing the drug's bioavailability. By employing the film-forming chemicals HPMCE5 and PVA, buspirone fast-dissolving oral films were created from nanosuspensions. Buspirone oral film shown outstanding physic mechanical properties, high stability, and burst release followed by sustained drug release in in vitro experiments [128, 143]. Many weakly water soluble medications might have their dissolution and permeability properties improved by adding nanoparticles to fast-dissolving oral films. The antisolvent evaporation approach was used to create rapidly dissolving oral films containing nanoparticles of the medication lercanidipine, which is poorly soluble in water and has a limited bioavailability [143, 144].

Maltodextrins were used as the film-forming material and glycerin served as the plasticizer in feasibility experiments of low bioavailable, quickly dissolving oral films containing quercetin, which showed that the addition of nanocrystals had no effect on the elasticity and ductility. It was discovered that the dissolving rate was higher than that of bulk drugs. The Tmax and Cmax of lutein nanocrystals fast-dissolving oral films in rats were significantly lower than those of oral solution, according to pharmacokinetic studies. Additionally, the nanocrystal fast-dissolving oral films' AUC0-24h was around 2-times greater than that of the oral solution, demonstrating the considerable increase in the rate and breadth of bioavailability [73, 27, 129].

Recently, a mucoadhesive film based on nanosuspension that contains carvedilol was created and sandwiched between backing and mucoadhesive layers. Using PEG400 as a plasticizer, nanosuspension was added to a hydrogel made of HPMC and Carbopol 934P. When compared to commercial tablets, in vivo investigations on rabbits showed a considerable increase in the relative bioavailability [145].

13. Application of nanosuspension DDS

Nanosuspension has the ability to address the issues related to the delivery of medications that are poorly lipid - and water-soluble due to the reduction in particle size and increase in surface area [17]. The oral pulmonary, parenteral, and ocular drug delivery areas have seen extensive use of the nanosuspension DDS, which has shown great advantages over conventional drug administration routes. In the section that follows, several uses of nanosuspension DDS will be addressed [83].

13.1 Oral drug administration [146-148]

Due to the many benefits, it offers, the oral administration route is favored above the many alternative medication delivery methods. These benefits include dependability to adapt different medication kinds, safety, excellent patient compliance, simplicity of intake, pain avoidance, and versatility. Drugs that are poorly soluble can benefit from oral administration of nanosuspension DDS to increase their bioavailability. The main factors are the numerous benefits of nanosuspension DDS for oral administration, including increased dissolution rate and solubility of poorly soluble drugs, high drug nanocrystal adhesiveness on the epithelial gut wall, prolonged drug nanocrystal absorption time due to the length of the gastrointestinal tract, and reduced variability caused by food. For oral administration, it is possible to use both liquid dosage forms and solid dosage forms, such as powder, tablet, pellet, capsule, and film. You can use the produced liquid nanosuspensions for oral administration in liquid dose form right away.

13.2 Intravenous administration [147-149]

The parenteral method of administration offers the drug's fast targeting, quick beginning of action, and decreased dose. For medications undergoing first-pass metabolism as well as those that are not absorbed in the GIT or that are degraded in the GIT, this is the recommended route. The creation of intravenously given goods is one of the key uses of nanosuspension technology. Aside from targeting macrophages and the harmful germs that live inside them, administering pharmaceuticals that are poorly soluble by IV has various other benefits, including increasing the therapeutic efficacy of medications that are already accessible in normal oral formulations. When Peters et al. created clofazimine nanosuspensions for intravenous administration, they found that the drug concentrations in the liver, spleen, and lungs were comparable higher and much beyond the minimal inhibitory concentration for the majority of Mycobacterium avium strains.

The study also shows that the liver collected more of the nanoparticle formulation than the liposomal formulation, suggesting that the nanoparticle formulation has higher targeting capability. To overcome the limited effectiveness gained using traditional solubilization strategies, such as usage of surfactants, cyclodextrins, etc., to increase bioavailability, injectable nanosuspensions of the weakly soluble medication tarazepide have been developed. Omeprazole has been produced into a stable intravenously injected formulation to stop it from degrading when taken orally.

13.3 Parenteral administration [129, 147, 149]

In some cases, parenteral administration is favored over other medication delivery methods, such as in cardiac arrest and anaphylactic shock emergencies. This method of administration has a number of benefits, including avoiding first-pass metabolism, improved bioavailability, and consistent dose. Parenteral delivery, which offers better control over the dosage and pace than oral administration, results in more predictable pharmacodynamic and pharmacokinetic characteristics. Typically, the size of medication particles delivered should be less than 5 m to prevent capillary occlusion. It was shown that oridonin in the form of nanosuspension may significantly increase the rate of tumor inhibition by about 20% when compared to the standard form of oridonin in a study on the evaluation of oridonin nanosuspension's capacity to inhibit tumor development. With the use of nanosuspension, therapeutic effectiveness is increased while costs are significantly decreased.

13.4 Pulmonary drug delivery [143, 150]

Asthma and chronic obstructive lung disorders can both be treated extremely well with pulmonary medication delivery. The delivery of drugs via the lungs has benefits over the parenteral and oral routes listed above. When administered through the lungs, the medication is brought right up close to the area of action. The need for a lower dosage is reduced, and adverse effects are lessened. Numerous issues with traditional pulmonary medication delivery exist, including a lack of selectivity, fast drug release, and poor drug residence duration. The issues of low drug solubility and a lack of selectivity can be remedied by adopting the nanosuspension approach to deliver the medicine directly to afflicted pulmonary cells. Since nanosuspensions adhere to mucosal surfaces more firmly, they spend longer at the target region, increasing selectivity and significantly lowering drug loss. As a result of the nanosuspensions' capacity to speed up drug diffusion and breakdown while preventing unfavorable drug deposition in the mouth and throat, pulmonary administration methods often result in enhanced bioavailability of the administered medication.

13.5 Ocular administration [31, 66, 150]

The use of repeated instillations, poor drug solubility in lachrymal fluids, and other drawbacks of traditional eye therapeutic techniques include a host of unwanted side effects. The use of nanosuspensions can get around these drawbacks of the traditional administration technique. This nanosuspension method has several benefits, including extending the drug's duration in the eye and significantly increasing bioavailability. Additionally, the drug release can be prolonged due to the high attachment of positively charged nanoparticles in nanosuspension to negatively charged mucin. For instance, chitosan, a mucoadhesive cationic polymer, is used in ocular medication delivery to bind to negatively charged mucin, considerably extending the drug residence period. Drug loss may be reduced thanks to the drug nanoparticles' inherent adhesiveness.

13.6 Dermal delivery [149-151]

The nanocrystals show better permeation and bio-adhesiveness as a result of higher nanocrystal penetration into a membrane. Investigations into injectability and rapid dissolving are necessary to create intravenous formulations. Years of study have gone by with little success in using adhesion, rapid dissolution, or improved penetration for cutaneous and mucosal applications. In order to boost the penetration of drug nanocrystal, the concentration of the poorly soluble drug was raised. This may have increased the concentration gradient between the formulation and the skin. It was discovered during research on a penetration barrier that lutein nanocrystals have a fourteen-fold more capacity than raw powder to pass through cellulose nitrate membranes. However, due to the lipophilicity of lutein, these nanocrystals remained in the pig ear skin after entering.

13.7 Targeted drug delivery [75, 126, 150]

By adjusting the particle size, drug nanoparticle absorption in vivo behavior may be tailored. Surface characteristics alter as a result of changes in particle size. As a result, the method of nanosuspension may be employed for targeted distribution. To prevent nanocrystals from being phagocytotic ally taken up by cells, smart crystal drug particles smaller than 100 nm can be utilised in the DDS. Due to its simplicity, developing nanosuspension for targeted medication administration is possible. A mucoadhesive nanosuspension was reportedly utilised to target Cryptosporidium parvum. The surface characteristics of the drug particles, such as surface hydrophobicity, charge, and the presence and concentration of certain functional groups, affect how the drug particles are distributed throughout the body. Thus, the discovery that Tween 80-coated nanocrystals may be employed for brain targeting is unexpected. A noteworthy example is the use of atovaquone nanocrystals coated in Tween 80 to treat toxoplasmosis.

13.8 Bioavailability enhancement [151, 152]

Low bioavailability of medications may be caused by factors such as their poor solubility, permeability, and stability in the gastrointestinal tract (GIT). The issue of poor solubility and poor permeability across the membrane can be remedied by converting the drug particles into nanosuspensions. With instance, oral administration of the gonadotrophin inhibitor Danazol nanosuspension can result in an absolute bioavailability of 82.3% as opposed to just 5.2% for traditional dispersion. According to Kayser et al., Amphotericin B nanosuspension significantly improved oral absorption when compared to the drug's standard formulation. Oleanolic acid is a weakly soluble hepatoprotective drug, and the application of a nanosuspension increased bioavailability. Significantly increased therapeutic impact suggested increased bioavailability. In comparison to the dissolution from a coarse powder (15% in 20 min.), the nanosuspension disintegrates faster (90% in 20 min.).

14. Marketed products [55]

Route	Drugs	Therapeutic class	Company/author
Oral route	Carbamazepine Megestrol acetate Paliperidone palmitate Insulin Ketoprofen Azithromycin Albendazole Tarazepide Griseofulvin Mitotane Cilostazol Aphidicolin Buparvaquone Fenofibrate Cytokine inhibitor Emend Rapamune Probucol Danazol	Psycholytic Steroid hormone Anti schizophrenia Diabetes Analgesic Antimicrobial Anthelmintic drug Selective CCKa-antagonist Antifungal Adrenal Cortex Hormones cagent Antileishmanial Antibiotic Lipid lowering Crohn's disease Anti-emetic Immunosuppressant Lipid lowering Hormone	D. Douroumis Par Pharmaceuticals Johnson and Johnson BioSante Remon J. P. Dianrui Zhang Mittapalli P. K. C. Jacobs Boris Y. Shekunov Michele Trotta Jun-ichi Jinno O. Kayser Müller R. H. SkyePharma Elan Nanosystems Elan Nanosystems Elan Nanosystems Jyutaro Shudo Rogers T. L.
parental	Naproxen	Anti-inflammatory	Anchalee Ain-Ai
Intravenous	Loviride Clofazimine Oridonin Ascorbyl palmitate Dihydroartemisinin Omeprazole Thymectacin Paclitaxel	Antivirotic Antimycobacterials Anticancer Antioxidant Antimalarial Proton pump inhibitor Anticancer Anticancer	B. Van Eerdenbrugh K. Peters Lei Gao Veerawat T. Jiraporn C. Jan Möschwitzer Elan Nanosystems American Bioscience
Ophthalmic	Hydrocortisone Prednisolone Hexadecadrol	Glucocorticoid	M. A. Kassem
Pulmonary	Budesonide Fluticasone	Asthma	Jerry Z. Yang
Intrathecal	Busulfan	Anticancer	SkyePharma
topical	Silver	Eczema	Nucryst

Table 1: nanosuspension product which are marketed in country.

15. Challenges and future perspectives

Drug nanocrystals, regardless of how they were created, are a technique that can be used to any poorly soluble medications to solve their solubility and bioavailability issues. Any drug may be converted into drug nanoparticles, which has the general property of increased adhesiveness to surfaces and increases saturation solubility and dissolution velocity [153-155]. By creating mucoadhesive nanosuspensions for oral use or surface-modified site-specific nanoparticles for intravenous injection, surface modification of the drug nanocrystals can further boost the advantages (e. g. targeting to the brain, bone marrow etc.). Another benefit is the ability to combine this cutting-edge nanosuspension technology with conventional dosage forms, such as incorporating medication nanoparticles into pellets or tablets for oral administration. The technology's ease of use is a standout quality. The likelihood of introducing items to the market increases with system simplicity. The quantity of goods that will be available on the

market in the near future will serve as evidence of the success of drug nanoparticles, particularly the third generation of product nanosuspensions [155-157].

Safety, effectiveness, and stability are three of a drug's most fundamental and important qualities. Additionally, stability was somewhat dependent on safety and effectiveness. Additionally, strong stability is a guarantee of consistent safety and effectiveness [49, 33]. As a result, a very significant and crucial feature of this technique is the stability issue of nanosuspensions in drug administration. Although the technology of nanosuspensions has been thoroughly investigated recently, its use in the pharmaceutical industry is still limited. One significant challenge for this has been identified as the stability issue of nanosuspensions. The incompatibility between the instability of nanosuspensions and the requirement to achieve the stability standard required by the pharmaceutical industry will encourage the advancement of nanosuspensions technology [156-159].

This is the first special study that specifically addresses the stability problems with nanosuspensions in drug delivery, as far as we are aware. However, there were still a number of unidentified variables that may affect how stable nanosuspensions were. In general, nano- and micro-suspensions have several characteristics. In order to improve the stability of nanosuspensions, it may be possible to apply the information that has been studied for improving the stability of micro-suspensions, such as reducing density difference and raising viscosity. Due to the large physicochemical differences between nano- and micro-suspensions, there are regrettably still many obstacles in the way of the development of nanosuspensions technology [159-163].

Retrieving and developing stabiliser usage guidelines will likely become more and more important as nanosuspensions technology advances. A crucial and significant aspect of the formulation of nanosuspensions is the stabilizing capacity of the stabilisers, which determines the smallest attainable particle size and consequent physical stability. Since irreversible aggregation will limit the potential benefits of the nanosuspensions, such as improved dissolving velocity and saturation solubility, the physical stability of the nanosuspensions is also crucial [154]. The first tactic is to learn more about how to use the stabilisers that are now on the market. The majority of recent papers on nanosuspensions stabilisers were dispersed with no discernible themes. The second option is to create novel stabilisers that are more suited and more adaptable for making nanosuspensions, including biocompatible polymers of amino acids [163-168].

In addition to the developments in stabilisers, other factors are also crucial. These include, but are not limited to, solidification techniques and innovative preparation methods including multi-inlet vortex mixing technique (MIVM) [169]. The most recent research on nanosuspensions has largely concentrated on the effectiveness of preparation techniques, in vitro solubility and dissolution rates, and in vivo pharmacokinetics and pharmacodynamics [170]. The generation, stability, and overall effectiveness of nanosuspensions are therefore greatly influenced by the stabilisers. For the development of stabilisers, there are two methods. Therefore, it is important to demonstrate how the preparation method affects the stability of nanosuspensions. And the development of nanosuspensions technology is similarly prone to and constrained by this [171].

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