DOI: 10.55522/ijti.V1I3.0014 November - December 2023, Vol. 1 - Issue 3 ISSN NO: 3048 - 4626

IJTI | INTERNATIONAL JOURNAL OF THERAPEUTIC INNOVATION

Review article

Nanosuspension: an emerging nanotechnology for drug delivey system

Shweta Singh*, Shweta Jain

Sir Madanlal Institute of Pharmacy, Etawah, Uttar Pradesh, India

Corresponding author: Shweta Singh ✉ aniketiit01@gmail.com, **Orcid Id**: 0000-0001-8955-1981

Received - 05-12-2023**, Revised** - 14-12-2023, **Accepted** - 22-12-2023 **(DD-MM-YYYY)**

Refer this article

Shweta Singh, Shweta Jain. Nano suspension: an emerging nanotechnology for drug delivey dystem international journal of therapeutic innovation, Nov-Dec 2023, V 1 - I 3, Pages - 0053 – 0063. Doi: https://doi.org/10.55522/ijti.V1I3.0014

ABSTRACT

Now a day's nanotechnology is one of the advancement technique within the fields of medication. "Nano" way very small in length the particle length starting from 1-a thousand µm. Nano suspensions is particularly developed era within the subject of nano technological know-how. A pharmaceutical nano suspension is described as a totally finely colloid, biphasic, dispersed, solid drug particles in aqueous car, size beneath 1µm, without any matrix cloth, stabilized through surfactants & polymers, prepared through suitable techniques for drug shipping applications, by means of distinctive approaches of routes of administration like oral, topical, parenteral, ocular & pulmonary routes. A nano suspension no longer only solves the troubles of bad solubility and bioavailability, but additionally alters the pharmacokinetics of drug and for that reason improves drug protection and efficacy. Low bioavailability is one of the essential drawbacks associated with capsules which show negative aqueous solubility. The problem is even greater complex for capsules belonging to BCS class II as categorized with the aid of BCS classification system, showing negative solubility. Solubility in each aqueous and nanoqueous media including tablets like carbamazepine, itraconazole and so forth. Nano suspension, is an advancement era overcome those troubles concerning solubility.

Keywords: Bioavailability, Nanoparticle, Colloidal dispersion, Drug delivery, Nanosuspension, Solubility.

INTRODUCTION

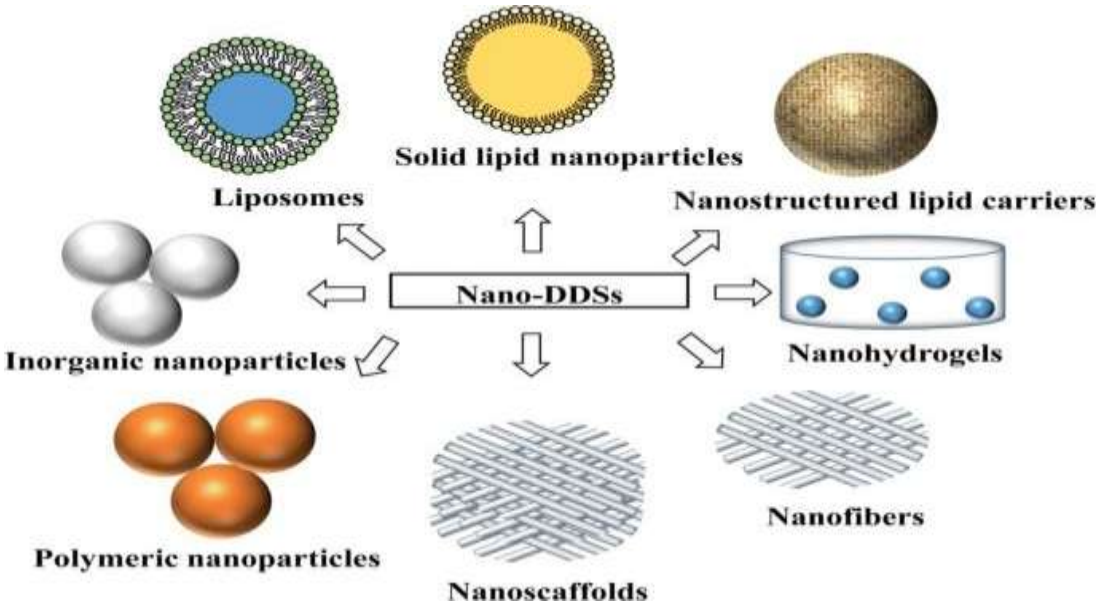
A massive wide variety of drugs had been found to possess solubility issues each in aqueous and non-aqueous media because of negative bioavailability due to low solubility, drug effectiveness is also affected the difficulty of bioavailability can be attributed to insufficient solubility or permeability. With the advancement of technology, the need of advancement of pharmaceutical technology has additionally been increasing [1]. Improvement of a brand new formula is majorly attributed to parameters which includes solubility and stability of the drug at ambient temperature[2].Therefore, diverse tactics were made in growing new formulations to enhance the solubility and bioavailability of those capsules. It's been observed that poorly water-soluble tablets pose many troubles in formulating it right into a traditional dosage shape. One of the vital problems associated with the ones capsules is erratic absorption[3]. Many strategies were developed to improve the dissolution fee of these tablets.Consequently, within the last few decades, the enhancement of bioavailability of poorly water-soluble pills has emerge as the main target of drug improvement.

A completely not unusual way of growing drug solubility is particle length reduction. The drug particle floor region is also enhanced by micronization, which produces particles in the size range of 2 µm to five µm. but, micronization by myself every now and then won't be sufficient to increase competently the drug dissolution fee and absorption within the gastrointestinal tract as in case of poorly soluble drug[4]. A few other techniques had been developed related to the optimization of the dissolution rate of those drugs with solubility issues like particle length discount, solubilization, salt formation, and preparation of

solid dispersion structures. But, there are sure disadvantages related to the production of nanoparticle that limits the usage of nanosuspension techniques. Especially, the particle length discount approach leads to deterioration of a few powder residences, inclusive of their glide homes and wettability, even as improving the development of electrostatic forces, main to suspicious formulations. Some of negative aspects are also associated with this method along with wide particle length distribution, infection of drugs, crystal structures version, and uncontrolled particle morphology and so on. In the last few years, bottom-up technologies together with supercritical fluid (SCF) approach and liquid precipitation which are concerned in manufacturing of ultrafine drug debris, together with clarithromycin, olanzapine, paclitaxel, and many others have been broadly investigated for their efficient performance inside the discipline of nanotechnology. Even though advanced technologies like emulsions, micro emulsions, liposomes, stable dispersion technology and inclusion complexes using cyclodextrins are to be had now days to formulate water-insoluble drugs, however there's no frequent approach applicable to all pills. Therefore, to triumph over the formulation-related troubles a specific strategy is wanted for improvement of its scientific efficacy on the way to optimize their Pharmacoeconomics worries [4, 5]**.** This novel era has been capable to expose their capacity to adjust and improve the troubles associated with the BCS class II pills and are precise because of their simplicity and the advantages they confer over different formula. This novel generation keeps the desired crystalline nation, which leads to stepped forward dissolution price and advanced bioavailability[6]**.**Consequently, it additionally help to lessen the dose of conventional oral dosage shape.[7]

A pharmaceutical nanosuspension is described as "very finely colloid, biphasic,discrete strong drug particles in an aqueous vehicle, stabilized through way of surfactants, for both parenteral and pulmonary administration[8], oral and topical use or with decreased particle length, leading to a better dissolution charge and consequently expanded bioavailability."The diameter of the suspended particle is much less than 1micrometer in length. The particle length distribution of the strong particle in nanosuspensions is generally much less than one micron with a mean particle length ranging between 200 and 600nm.An upturn inside the the dissolution charge of micronized debri is related to an increase in the surface and consequently the dissolution speed. Nanosize debris can growth dissolution pace and disolution velocity because of the vapour stress impact [8, 9].

Figure 1: Drug Delivery System

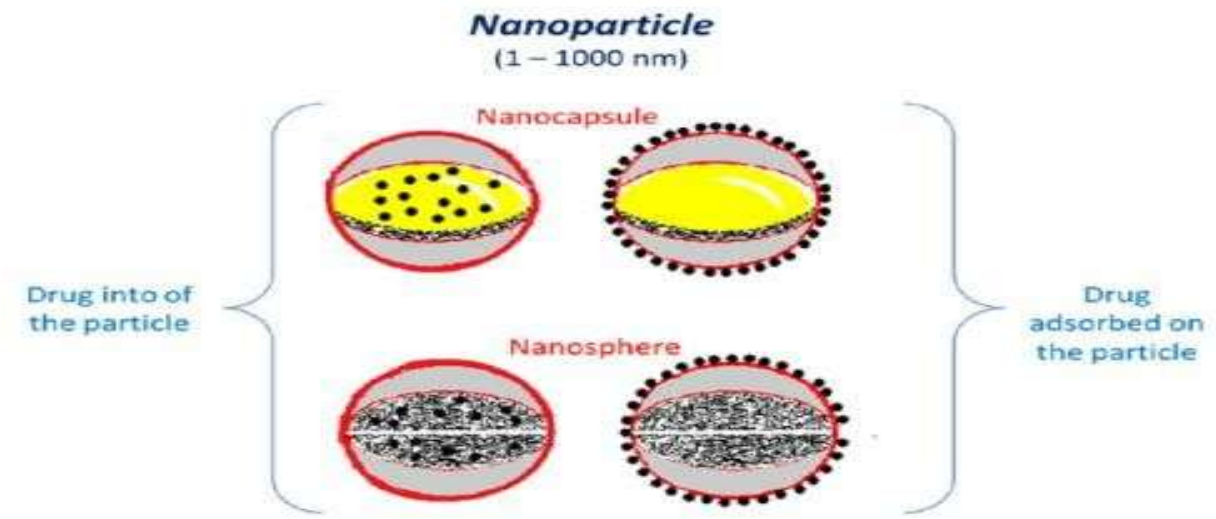


Need of Nano-suspension

More than forty% of drugs are poorly soluble in water, in order that they display problems in formulating them in conventional dosage paperwork. Also, for class II pills that are poorly soluble in aqueous and natural media, the problem is extra difficult. Making ready nanosuspension is selected for such compounds that are insoluble in water (however are soluble in oil) with high log P-value. numerous strategies to remedy problems of low solubility and occasional bioavailability micronization, solvency, oily solution, salt formation- some different techniques are liposomes, emulsions, microemulsion, solid dispersion,

ßcyclodextrin inclusion complicated, and so forth but, many of these strategies aren't universally applicable to all tablets [3].In those cases, nanosuspensions are favored. Inside the case of drugs which can be insoluble in both water and inorganic media in its vicinity of the use of lipidic structures, nanosuspensions are used as a formulation method. It's far maximum appropriate for the compounds with high log P cost, high melting factor, and high dose. Nanosuspensions can be used to improve the solubility of medication that are poorly soluble in aqueous as well as lipid media. As an end result, the fee of flooding of the lively compound rises, and the maximum plasma degree is reached quicker (e.g., oral or intravenous (IV) administration of the nanosuspension). This is one of the ordinary blessings that it has over other methods for growing solubility. It's far beneficial for molecules with terrible solubility, poor permeability or each, which poses an important challenge for the formulators. Fundamental problems related to poorly water-soluble compounds four. although all marketed products currently are produced by means of so-referred to as „pinnacle-down strategies", in which the nanoparticles are discovered via length discount into the submicron-range, bottom-up techniques and mainly managed precipitation methods these are techniques for the canonization of poorly soluble capsules. In this method, with none harsh situations and handle with easy forms of device, one could lesser the particle size to a few hundred nanometers variety. Therefore, all that technique is used for the production of nanosuspension, a cautious evaluation of the kind and attention of the stabilizer is an extreme stage for the hit production of nanosuspension. Each polymeric and surfactant stabilizers can be used for this reason. Nanosuspensions vary from Nanoparticles, which are polymeric colloidal providers of medication (Nanospheres and nanocapsules), and from strong lipid nanoparticles (SLN), that are lipidic vendors of the drug. The important thing amendment from conventional formulations of suspensions is that the particle length distribution of the strong particles in nanosuspensions is commonly less than 1 µm (i.e., 0.1nm1000nm), with a mean particle length variety among 2 hundred–six hundred nm. On the other hand, the particle diameter crucial in most right pharmaceutical suspensions is 1 to 50 µm. In nanosuspensions, the general bioavailability is improved by an increase in surface vicinity and saturation solubility via particle size discount [5].

Figure 2: Nanoparticle



Major Advantages of Nanosuspension [9]

- ✓ Its popular applicability to the maximum pills and its simplicity.
- ✓ It is able to be useful for poorly water-soluble tablets.
- ✓ Possibility of significant production, the pre-requisite for the introduction of a delivery system to the market[4]

Disadvantage of nanosuspension [9, 10]

- ✓ Dose accuracy and uniformity is difficult to maintain.
- ✓ Sedimentation and Compaction may pose problems.
- ✓ Must be handled carefully during transportation.
- ✓ **Formulation Consideration**
- ✓ Nanosuspension formulation requires basically stabilizer or surfactant, proper solvent system, and other ingredients for its preparation.

Stabilizer

Stabilizer plays an essential position inside the method of nanosuspensions. In the absence of an appropriate stabilizer, the excessive ground power of Nanosize particles

can result in agglomeration or aggregation of the drug crystals. The most essential feature of a stabilizer is too moist the drug debris genuinely and to stop Ostwald's ripening and agglomeration of nanosuspensions so one can yield a stable bodily formula with the resource of providing steric or ionic obstacles. The sort and quantity of stabilizer have a said effect on the bodily balance and in-vivo conduct of nanosuspensions. In a few instances, an aggregate of stabilizers is needed to gain a solid nanosuspension. The drug-to-stabilizer ratio inside the additives can also vary from 1:20 to 20:1 and want to be investigated for a unique case. Example: lecithin's, PVPK30, PVA, SLS. Cellulosics, two Poloxamers, Polysorbates, Lecithin, and two Povidones [6].

Organic Solvents

Organic solvents are normally used inside the training of nanosuspension if emulsion or micro emulsions technology are used because the template for this. These solvents are very hazardous in physiologic and environmental means; but, nevertheless, some much less unsafe water-miscible solvents like methanol, ethanol [7].

Surfactants

Surfactants are integrated to enhance the dispersion with the aid of reducing the interfacial tension. They also act as wetting or deflocculating agents. Example: Tweens and Spans - broadly used surfactants [6].

Co-surfactants

The desire of cosurfactant is crucial while the use of microemulsions to formulate nanosuspensions. Seeing that co-surfactants can appreciably have an effect on segment behavior, the effect of co-surfactant on uptake of the inside phase for selected microemulsion composition and on drug loading ought to be investigated. Instance: Transcutol, glycerol, ethanol, and isopropanol bile salts and Dipotassium glycyrrhizinate may be used as co-surfactants [6].

Other Additives

Nanosuspensions may comprise additives such as buffers, salts, polyols, cosmogenic, and cryoprotectants, depending on both the route of administration and the properties of the drug moiety[3].

Properties of Nanosuspension

Long-Term Physical Stability

Ostwald ripening is chargeable for crystal increase and subsequently, formation of micro particles. Ostwald ripening was introduced on thru the variations in dissolution strain/saturation solubility among small and large debris. Molecules diffuse from the higher concentrated place round small debris (higher saturation solubility) to regions round larger particles owning decrease drug attention. This leads to the formation of a supersaturated solution across the huge particles and, consequently, to drug crystallization and increase of the large debris. The diffusion method of the drug from the small debris to the large particles leaves an area around the small particles which might be now not saturated any greater, because of this main to the dissolution of the drug from the small particles and in the end completes the disappearance of the small debris [8].

Internal Structure of Nanosuspension

The excessive-strength enter for the duration of the disintegration method reasons structural modifications within the drug debris. While the drug particles are exposed to excessive-strain homogenization, debris are transformed from a crystalline nation to an amorphous kingdom. When the drug debris are uncovered to excessive-strain homogenization, particles are converted from a crystalline kingdom to amorphous country. The exchange in the kingdom is predicated upon the hardness of the drug, quantity of homogenization cycles, chemical nature of the drug, and electricity density applied via the homogenizer [8].

Adhesiveness

There may be a distinct growth within the adhesiveness of ultra-first-class powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for elevated oral shipping of poorly soluble tablets. A substantially high-quality file is that ofexpand in bioavailability for diazole from 5% (as micro suspension) to 82% (as nanosuspension) [5].

Nanosuspension Enhance Bioavailability

Drug with terrible solubility, bad permeability or negative solubility inside the gastrointestinal tract will cause negative oral bioavailability. Nanosuspension resolves the trouble of negative bioavailability through solving the trouble of negative solubility, and poor permeability during the membranes.

Benefits of nanosuspensions over conventional formulations in different routes [11]

1 Oral: Rapid onset of action/ improved solubilities so improved bioavailability

2 Ocular: Higher bioavailability/ dose consistency

3 Intravenous: Rapid dissolution/tissue targeting.

4 Intramuscular: Reduced tissue irritation

5 Inhalations: Rapid dissolution/high bioavailability/dose regulation

Techniques for preparation of nanosuspension

Bottom-up technology

Bottom-Up technique is one of the traditional strategies of precipitation (Hydrosols). In this approach, the drug is dissolved in an organic solvent and this answer is mixed with a miscible antisolvent. Inside the water-solvent mixture and the drug precipitates because of low solubility. Precipitation has also been inclusive of excessive shear processing. The Nano area system is based at the precipitation of friable materials for next fragmentation under conditions of high shear and/or thermal energy. This is executed with the aid of combining each rapid precipitation and high-pressure homogenization techniques. Rapid addition of a drug strategy to an antisolvent finally ends up in surprising supersaturation of the combined solution and era of high-quality crystalline or amorphous solids. Precipitation of an amorphous fabric may be preferred at high supersaturation whilst the solubility

Of the amorphous state is handed this has the gain of the

Usage of exceptionally simple and occasional-value device.

However, this created problems in stirring and mixing when haunted for large-scale production. The major challenge of this technique is to avoid crystal growth that occurs in storage due to Ostwald ripening [3, 4, 5, and 15].

Top- down technology

1. **Nanoedge** This technology follows the precept of precipitation and homogenization. This generation helps to reap smaller particle length and higher balance inside a short period of time. Nano edge generation also helps to conquer the drawbacks related to precipitation technique consisting of crystal boom and long-time period stability.
2. **Nanojet** It is also known as opposite stream technology, where a stream of suspension is divided into two or more parts in a chamber and particle size gets reduced due to high pressure collision produced during the process. M110L and M110S microfluidizers (Microfluidics) are example of few equipment using this technology. Nanosuspension of atovaquone is prepared using the micro fluidization process. However, despite of being an advantageous novel technique it has got few disadvantages. The major one being the higher number of passes through the microfluidizer, and also the final product contains a relatively larger fraction of microparticle [9,16,17].

Figure 3: Bottom up technique

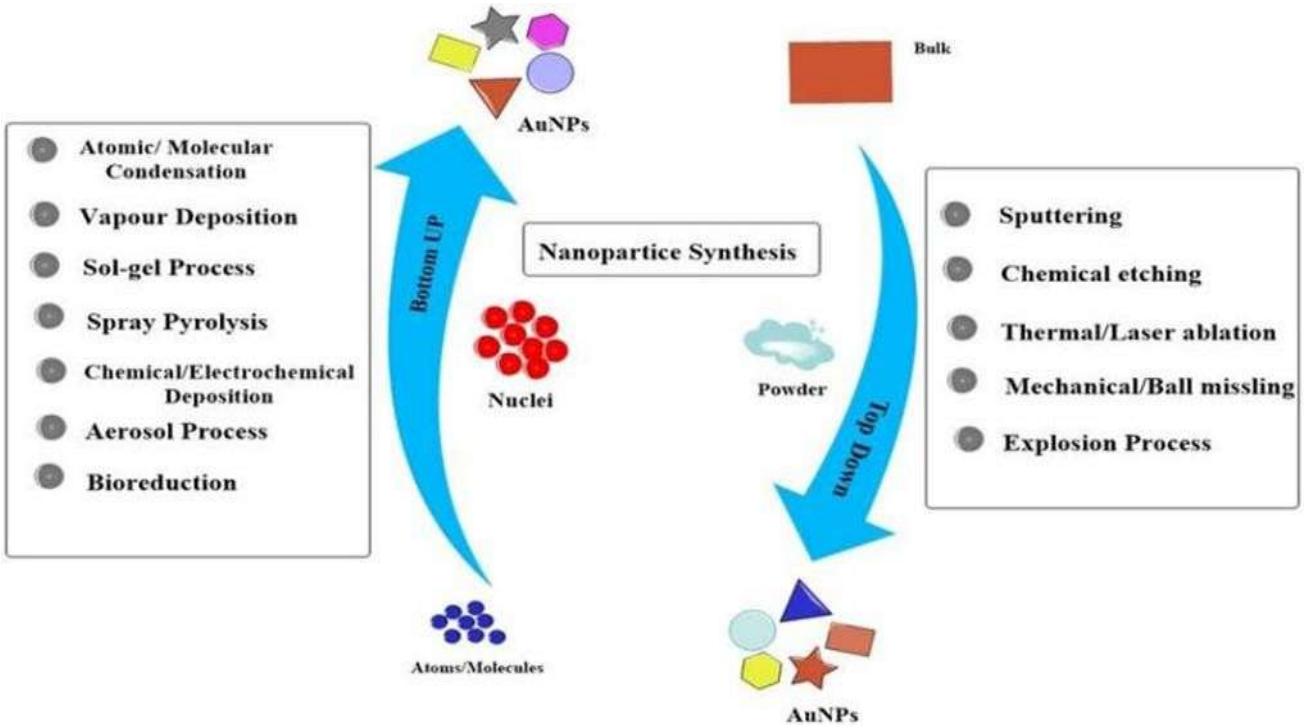
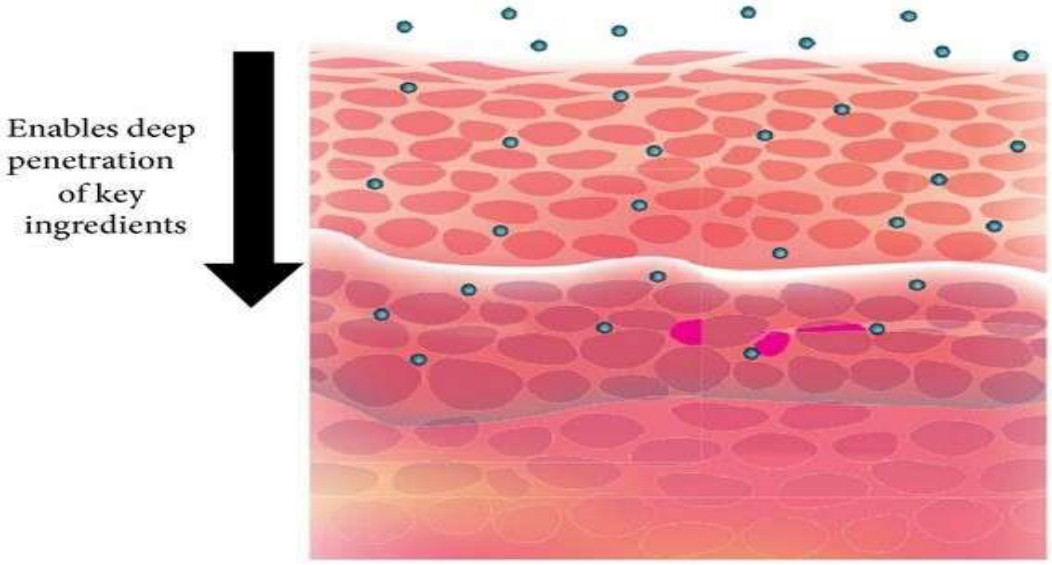


Figure 4: Nano sspension technology



Nanosuspension technology

Media milling (Nanocrystals or Nano systems)

Liversidge et.al developed media milling technique for the first time. This technology utilizes high-shear media mills or pearls Media milling for the production of nanosuspension. Here, the drug is subjected to media milling where a high energy and shear forces are generated as a result of the impaction of the milling media. This whole process provides the necessary energy input to disintegrate the solid drug particles into nanosized particles. In this process, the milling chamber is charged with the milling media, drug, a suitable buffer or water and stabilizer. Then the instrument is rotated at a very high shear rate. The major disadvantage associated with this technique is the residues remaining in the finished product could be problematic for administration [4, 9].

Dry co-grinding

From the various studies on nanosuspensions, it has been found that dry milling technique has also come out as very helpful technique to produce nanosuspension. It has been reported that using dry co-grinding technique, stable nanosuspensions of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media could be prepared successfully. Colloidal suspension of poorly soluble drugs like griseofulvin, glibenclamide, and nifedipine with solvents such as polyvinylpyrrolidone (PVP) and sodium dodecyl sulfate (SDS) are prepared by dry co-grinding method. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives have also been used in this system. Co grinding can also improve the physicochemical properties as well as the dissolution of poorly water-soluble drugs by working on its surface polarity and transformation from a crystalline to amorphous form. Further, dry co-grinding is a easy and economic technique which can be conducted without organic solvents [18].

Lipid emulsion/microemulsion template

Nanosuspensions can also be produced by conventional method such as emulsion using a partially water-miscible solvent as the dispersed phase. Microemulsions as templates can also produce nanosuspensions. They are thermodynamically stable and isotopically clear dispersions of two immiscible liquids which is stabilized by an interfacial film of surfactant and co-surfactant. The preformed microemulsion can be saturated with the drug by intimate mixing or the drug can also be loaded into the internal phase of the same. A Suitable dilution of the emulsion yields nanosuspension. For example, nanosuspension of griseofulvin with lecithin, butyl lactate, water and the sodium salt of taurodeoxycholate is prepared by the microemulsion technique. The advantages of this technique as templates for nanosuspension formation are that easy production of nanosuspension by controlling the emulsion droplet and easy for scale-up. However, the use of organic solvents affects the environment and large amounts of surfactant or stabilizer are required [10].

Supercritical fluid process

The supercritical fluid process is another method through which nanosized particles are obtained by solubilization and nanosizing techniques. Through the process drug particles can be micronized to the submicron level. Supercritical fluids (SCF) are noncondensable dense fluids, the temperature and pressure of which is greater than its critical pressure (Tp) and critical temperature (Tc). It has been reported that recent advancement in the SCF technology is to create a nanoparticulate suspension of particle size of 5 to 2000nm in diameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry [9, 19].

Emulsification-solvent evaporation [20]

In the solvent evaporation technique, volatile solvents and emulsions area unit accustomed build the chemical compound resolution. Within the past, solutions like methylene chloride and chloroform were used that have currently been replaced by ester having a higher pharmacology profile. On evaporation of the solvent from the polymer, the emulsion is then converted into a nanoparticle suspension, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, the two main strategies involved are the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in water, (w/o)/w. Both the methods require ultrasonication or high-speed homogenization, followed by evaporation of the solvent, either under reduced pressure or by continuous magnetic stirring at room temperature. The ultracentrifugation method makes the solidified nanoparticle which are washed with Distilled water to clean it up from the additives like surfactants, and then it is lyophilized. The concentration of polymer, stabilizer, and the speed of homogenizer affected the size of the particle.

Melt emulsification method

In this technique, the drug is dispersed in the stabilizer which has been prepared in aqueous media. The dispersion is then heated above the melting point of the drug and then it undergoes homogenization to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with a temperature controller. Also the temperature of the emulsion was maintained above the melting point of the drug throughout the process. The emulsion was then allowed to cool down to room temperature either slowly or on an ice-bath. This technique has got the advantage of total avoidance of organic solvents during the production process. Nanosuspension of ibuprofen was prepared by this method [7,20].

Table 1: Summary of nanosuspension formation technologies and compounds produced in nanosuspension[4].

Technology	Advantage	Disadvantage	Drug
Precipitation	Simple technique equipment cost is low	-The Drug has to be soluble in at least one solvent and this solvent requires to be miscible with a non-solvent. -Growth of drug crystals requires to be controlled by addition of surfactant	Carbamazepine, Cyclosporine, Griseofulvin, Retinoic acid
High pressure homogenisation	applicable to most drugs -Can be Used for formation of very dilute as well as highly concentrated nanosuspension.-Simple technique-Aseptic production possible-Risk of product contamination	-High number of homogenizations cycles -Prerequisite for drug to be in micronized state and suspension formation before homogenization -Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer	Albendazole, Amphotericin Aphidicolin, Atovaquone Azithromycin, Budesonide Bupravaquone, Clofazamine Fenofibrate, Glucocorticoid drugs
Emulsion/ Microemulsion template	High drug solubilization -Long shelf life -Ease of manufacture	-Use of hazardous solvent -Use of high amount of surfactant and stabilizer	Breviscapine, Griseofulvin Ibuprofen, Mitotane
Media milling	Ease of scale up -Little batch to batch variation -High flexibility in handling large quantities of drugs	-Generation of residue of milling media -Require milling process for hours to days -Prolonged milling may induce the formation of amorphous lead to instability	Cilostazol, Danazol, Naproxen
Dry Co-grinding	Easy process -No organic solvent -Require short grinding time	-Generation of residue of milling media	Clarithromycin, Glibenclamide Glisentide, Griseofulvin, Naproxen, Nifedipine, Phenytoin, Pranlukast

Characterisation of Nanosuspension

Nanosuspensions are characterized for appearance, color, odor, assay, related impurities, particle size, zeta potential, crystalline status, dissolution studies, and in-vivo studies.

***In-vitro* Evaluation**

Mean Particle Size and Size Distribution

Various parameters of nanosuspensions like saturation solubility, dissolution velocity, physical stability, dissolution velocity, physical stability, and biological performance depend on the mean particle size and particle size distribution. Mean particle size and particle width (poly-dispersity index) can be decided through Photon Correlation Spectroscopy (PCS), laser diffraction, and colter current multi-sizer. The Poly-dispersity index (PI) be low for the long-term stability of the nanosuspensions. PI value of 0.1–0.25 shows a narrow size distribution, whereas a PI value larger than 0.5 suggests a very broad distribution. Due to the low measuring range (3nm to 3 μm) of PCS, the determination of the contamination of the nanosuspension (by drugs having a particle size greater than 3 μm) is difficult. So, to observe and quantify the microparticles that may have been generated in the course of the production process, laser diffractometry (LD) analysis should be carried out in addition to PCS analysis. Particles ranging from 0.05–80 μm and in certain units, particle sizes up to 2000 μm can be measured via using LD. Particle size analysis via the Coulter counter method is vital (in addition to PCS and LD) for nanosuspensions that are meant for intravenous administration. Coulter counter is a more efficient and appropriate method than LD analysis as it gives the absolute number of particles per volume unit for the different size classes. It quantifies the contamination of nanosuspensions through microparticulate drugs [1].

Particle Charge (Zeta Potential)

Zeta potential determines the stability of the nanosuspension. Both the stabilizer and the drug govern the zeta potential of a nanosuspension. Zeta potential of minimal ±30mV is required for electrostatically stabilized nanosuspension, and ±20mV is required in case of electrostatic and steric stabilization.

Crystalline State and Particle Morphology

It is necessary to know the crystal morphology of the drug in the nanosuspension. Polymorphic or morphological modifications in a drug that appears during nano-sizing can be determined via the information of crystalline state and particle morphology. The amorphous state of the drug formed during the preparation of nanosuspension is determined via X-ray diffraction analysis. It gives information about the adjustments in the physical state of the drug particles as well as the extent of the amorphous fraction. Differential scanning calorimetry can be used additionally. Scanning electron microscopy is additionally used to get exact information about particle morphology. The effect of high-pressure homogenization on the crystalline structure of the drug is estimated via X- ray diffraction analysis in aggregate with differential scanning calorimetry. Techniques like scanning electron microscopy (SEM), atomic force microscopy (AFM), or transmission electron microscopy (TEM) are preferred for determining the exact size and morphology of nanoparticles in suspension.

Saturation Solubility and Dissolution Velocity

The dissolution velocity and the saturation solubility are enhanced through the formula of nanosuspensions. Reduction in particle size results from the increased dissolution pressure and hence the solubility. Change in surface tension takes place as the solubility will increase (due to particle size reduction), which leads to increased saturation solubility. Different physiological solutions at different pH and different temperatures are used to carry out the determination of the saturation solubility and dissolution velocity according to the techniques suggested in the pharmacopeia. In-vivo overall performance (blood profiles, plasma peaks, and bioavailability) of the formulation is assessed by using these parameters. An increase in saturation solubility can be explained by using the Ostwald Freundlich equation [19]. Determination of the dissolution velocity of nanosuspensions gives information about the advantages of nanosuspension over conventional formulations, especially in sustained release dosage form The Ostwald-Freundlich equation is:

$$C(r) = C(\infty) \exp(2\gamma M / r\rho RT) \quad \text{Equation (1)}$$

Where C(r) and C (∞) are the solubilities of a particle of radius r and of infinite size. γ, M, and ρ are interfacial tension at the particle surface, the molecular weight of the solute, and the density of the particle, respectively [18].

Stability

Nanosuspensions Stability depends on the particle size of the suspended particles. The reduction in the particle size to the nano range will increase the surface energy of the particles, and the tendency of the particles to agglomerate increases. Therefore the stabilizers are used to reduce the chances of Ostwald ripening and to improve the stability of the suspension by means of providing a steric or ionic barrier. Stabilizers like cellulosic, Poloxamers, Polysorbates, lecithin, polyoleate, and Povidones are generally used in the nanosuspensions. Lecithin is desired in the improvement of parental nanosuspensions. Nanosuspensions can be stored at different stress conditions like distinctive temperatures (15, 25, 35 45°C), thermal cycling, and mechanical shaking and alternate in their mean particle size can be accompanied for three months. Different concentrations of small molecule surfactants (like sodium lauryl sulfate (SLS) and do fax 2A1 (DF)) and polymeric stabilizer (like Hydroxypropyl methylcellulose (HPMC)) can be evaluated to determine the effect of stabilizer type and micellar solubilized drug on Ostwald ripening [19].

PH: The pH of the nanosuspension can be easily measured by means of the use of a pH meter [20].

Osmolarity

Practically, the Osmolarity of nanosuspension can be measured by way of using Osmometer [20].

Drug Content

The drug content material of nanosuspension formulation can be carried out with the aid of extracting the nanosuspension in the appropriate solvent mixture, like Methanol: THF (1:1) mixture, shaken well and then centrifuged. The supernatants can be separated and diluted with the same solvent combination, and the absorbance can be measured at appropriate λmax. The drug content then can be calculated the usage of the calibration curve [20].

***In-vivo* Evaluation**

Particular drug and route of administration require the specific in-vivo evaluation of the nanosuspensions. Generally, the formulations are administered with the aid of the required route, and the plasma drug concentrations are decided via HPLC-UV visible spectrophotometry. Surface hydrophilicity/hydrophobicity (which determines interaction with cells prior to phagocytosis), adhesion properties, and the interaction with body proteins are normally evaluated via in-vivo parameters. The monitoring of the in-vivo overall performance of the Nanosuspensions and the establishment of the relationship between in-vitro release and in-vivo absorption are required in order to prepare a successful preparation. Irrespective of the route of the administration and the delivery systems. The rate of dissolution influences the in-vivo biological overall performance of oral nanosuspensions. The size of nanoparticle and surface properties of the particles determines the organ distribution for intravenously injected nanosuspensions. The invivo organ distribution conduct of the nanosuspension is affected by means of hydrophilicity/ hydrophobicity and interactions of particles with plasma proteins. Surface hydrophobicity is determined with the aid of hydrophobic interaction chromatography, and absorption of protein is determined by 2-D PAGE quantitatively and qualitatively after intravenous injection of nanosuspensions of the drug in animals.

Application of Nanosuspension

Nanosuspensions have a wide range of applications, especially in the case of low solubility and low bioavailability drugs. They are stated below.

Oral Drug Delivery

Because of the several benefits, the oral route is the preferable route for many of the drugs specified in the case of orally administering antibiotics such as atovaquone and buparvaquone. By making it in nano size, its solubility and bioavailability will increase. The oral administration of naproxen nanoparticles leads to an area below the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with naproxen nanosuspension and naproxen tablets 16. In the case of danazol (gonadotrophin inhibitor), nanosuspension has an absolute bioavailability of 82.3 and the traditional dispersion only 5.2% [21].

Parentral Drug Delivery:

Nanotechnology is additionally used in the parenteral drug delivery system. The advantage of this technique is it need only much less amount of toxic cosolvent for poorly soluble drugs. This will uplift the therapeutic effect of the drug compared with the conventional oral formulation and targeting the drug to the macrophages. The drug clofazimine is given as IV the concentration in the liver, spleen, and lungs reached an excessive level i.e.; higher than minimum inhibitory concentration, for most of the mycobacterium avium strains. Tarazepide is formulated as nanosuspension in order to

overcome the use of surfactants and cyclodextrins to improve the bioavailability [22].

Occular Drug Delivery

Certain drugs have poor solubility in the lachrymal fluid. If it is formulated as nanoparticles, its saturation solubility and bioavailability will increase. Mainly utilized to hydrophobic drugs. It increases the residence time in cul de sac. A great example of nanosuspension is ibuprofen. The anti-inflammatory activity of ibuprofen increased compared with the aqueous preparation [23].

Targeted Drug Delivery

Nanosuspensions also used for targeting their surface properties and altering the stabilizer can easily alter the in-vivo behavior. The drug will be uptaken via the mononuclear phagocytic system to allow regional specific drug delivery. This can be used for targeting antimycobacterial, fungal drugs to the macrophages. Atovaquone is used as targeting nanosuspension to the brain[2]

TABLE2: Current marketed formulations using nanosuspensions technology [25]

Drug	Product	Company/ Individual	Uses
Megestrol Acetate	MEGACE® ES	PAR Pharmaceutical	Appetite stimulant
Tizanidine	LA.Zanaflex	Acorda	To treat spasticity
Hydrochloride	CapsulesTM		
Morphine Sulphate	Avinza®	King Pharmaceutical	To treat moderate to severe pain that lasts for more than a few days
Dexmethylphenidate Hydrochloride	Focalin®XR	Novartis	Treatment of Attention Deficit Hyperactivity disorder
Sirolimus	RAPAMUNE®	Wyeth	Immunosuppressant
Fenofibrate	TriCor®	Abbott	Treatment of hypercholesterolemia
Aprepitant	EMEND®	Merck	Antiemetic
Fenofibrate	Triglide™	First Horizon Pharmaceutical	Treatment of Hypercholesterolemia
Methylphenidate Hydrochloride	Ritalin®	Novartis	Treatment of Attention Deficit Hyperactivity Disorder

CONCLUSION

Nanosuspensions seems to be a unique and yet commercially feasible method to combating such as poor bioavailability that is related to the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production strategies such as media milling and high-pressure homogenization has been efficaciously for largescale production of nanosuspensions. The advances in production methodologies the usage of emulsions or microemulsions as templates have provided still easier processes for manufacturing however, with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesive, versatility in surface modification and ease of postproduction processing, have widened the applications of nanosuspensions for various routes. The applications of nanosuspensions in parental and oral routes have been very well-investigated and applications in pulmonary and ocular delivery have been realized. However, their applications in topical, buccal, and nasal delivery are still looking ahead to exploration. Poor aqueous solubility is rapidly becoming the main hurdle for formulation scientists working on oral delivery of drugs compounds and leads to the employment of novel formulation technologies. The use of drug nanocrystals is a conventional formulation approach to increase the overall therapeutic performance of these drugs in any route of administration.

REFERENCES

1. Bhairav BA, Bachhav JK, Saudagar RB, 2016. Review on Solubility Enhancement Techniques. Asian Journal of Pharmaceutical Research. 6 (3), Pages 1-79Doi: 10.5958/2231-5691.

2. Khandbahale SV, 2019. A review- Nanosuspension technology in drug delivery system. Asian Journal of Pharmaceutical Research. 9(2), Page-130-138. Doi: 10.5958/2231-5691.

3. Patel M, Shah A, Dr.Patel NM, Dr.Patel KR, 2011. Nanosuspension journal of pharmaceutical science and bioscientific research, 1(1), Pages 1-10. Doi: 10.4103/2231-4040.82950.

4. Maria A, Cerdeira M, 2012. Production and Stabilization of Nanosuspensions of Poorly Soluble Drug Substances. Doi: https://doi.org/10.3929/ethz-a-007613986.

5. Sahu BP, Das MK, 2014. Nanosuspension for enhancement of oral bioavailability of felodipine Applied Nanoscience. (4), Pages 189–197 Doi: 10.1007/s13204-012-0188-3.

6 Chingupituk J, 2007. Nanosuspension Technology for Drug Delivery. Walailak Journal of Science & Technology. 4(2), Pages 139-153. Doi: 10.1007/s13204-012-0188-3

7 Koteswara K.B, Reddy MS, Naha a, Madhaban N, 2011. Nanosuspension: A novel drug delivery approach. International Journal of Research in Ayurveda and Pharmacy. (2), Pages 162-165. Doi: 10.4103/2231-4040.82950.

8. Pravakar CH, 2011. A review on nanosuspensions in drug delivery. International Journal of Pharma and Bio Sciences. 2(1), Pages 549 -558.

9. Patel VR Agarwal, 2011. YK Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology. 2(2), Pages 81-87. Doi: 10.4103/2231-4040.82950.

10. Kulkarni RR, Phadtare DG, Saudagar RB, 2015. A Novel Approach towards Nanosuspension. Asian Journal of Pharmaceutical, Research. 5(4), Pages 186-194 Doi: 10.5958/2231-5691.2015.00029.5.

11. Paun JS and Tank HM, 2012. Nanosuspension: An Emerging Trend for Bioavailability Enhancement of Poorly Soluble Drugs. Asian Journal of pharmacy and Technology. 2(4), pages 157-168. Doi: https://doi.org/10.1155/2015/938594.

13. Aher SS, Malsane ST, 2017. Saudagar RB Nanosuspension: An Overview. Asian Journal of Research in Pharmaceutical Sciences. 7(2), Doi: 10.2215/IJCPR.2017.V9I3.19584.

14. Phatak A, Jorwekar P. and Chaudhari PD, 2020. Nanosuspensions: A Promising Nanocarrier Drug Delivery System. Research journal of pharmaceutical dosage form and technology. 12 (3), Doi: 0.1211/0022357023691.

15. Eerdenbrugh BV, Mooter GV, Augustijns P, 2008, Top-down production of drug nanocrystals: Nanosuspension stabilization, miniaturization and transformation into solid product. International Journal of Pharmaceutics. 364(1), Pages 64-75 Doi: 10.1016/j. ijpharm.2008.07.023.

16. Rabinow BE, Thassu D, Deleers M, et al, 2007. Nanoparticuate drug delivery System: (Ed) informa Healthcare, New York, London. Doi: https://doi.org/10.1080/03639040701877119.

17. Kalimuthu S, Yadav AV, 2009. Nano-based Drug Delivery System: A Review. Research Journal of Pharmacy and Technology. 2(1), Page-21-27. Doi: 10.52711/2231-5691.2021.00023.

18. Jacob S, Nair AB & Shah J, 2020. Emerging role of nanosuspensions in drug delivery systems. Biomaterial Research. 24, Pages 3 Doi: 10.1186/s40824-020-0184-8.

19. Pawar P, Adhikrao Y, Varsha G., 2018. Different Techniques for Preparation of Nanosuspension with Reference to its Characterisation and various Applications - A Review. 8(4), Doi: 10.5958/2231-5659.2018.00035.8.

20. Elhissi A, Phoenix D, Ahmed W, 2015. Emerging Nanotechnologies for Manufacturing (Second Edition, William Andrew Publishing. Pages 402-417. Doi: 10.1016/B978-0-323-28990-0.00002-6.

21. Jacobs C, Kayder O and Muller, 2018. RH: Nanosuspension as a new approach for the formulation of poorly soluble drug tarazepide. Int J Pharma. (196) Pages 161-64. Doi: 10.1016/S0378-5173(99)00412-3.

22. Ponchel G, Montisci MJ, Dembri, et al, 2017. Mucoadhesion of colloidal particulate systems in the gastrointestinal tract. Ear J Pharm Biopharm. 44, Pages 25-31. Doi: 10.1016/S0939-6411(97)00098-2.

23. Chen Y, Liu J, Yang X, et al, 2017. Oleanolic acid suspension: preparation, in-vitro characterization and enhanced hepato-protective effect. J Pharma Pharmacol. (57), Page-259-26 Doi: 10.1211 /0022357055407.

24. Pu X, Sun J, Li M and He Z, 2016. Formulation of nanosuspensions as a new approach for the delivery of poorly soluble drugs. Current Nanoscience. (5), Page 417. Doi: 10.2174/157341309789378177.

25. Torchilin V, 2017. Hand Book of Nano biomedical Research. (3), Page-180.