



**NANOSUSPENSION: A NOVEL DRUG DELIVERY SYSTEM IN THE MIDDLE OF  
IMPROVED BIOAVAILABILITY**

Sonali S. Gadge<sup>1\*</sup> and Madhuri D. Game<sup>2</sup>

<sup>1</sup>P.R. Patil Institute of Pharmacy, Talegaon(SP), Ashti, Dist- Wardha 442202. (MS), India.

<sup>2</sup>Vidybharati College of Pharmacy, Amaravati- 444602 (MS), India.

**\*Corresponding Author: Prof. Sonali S. Gadge**

P.R. Patil Institute of Pharmacy, Talegaon(SP), Ashti, Dist- Wardha 442202. (MS), India.

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**ABSTRACT**

A pharmaceutical nanosuspension is all around finely colloid, biphasic, scattered particles in a fluid vehicle, measure underneath 1  $\mu\text{m}$ , with no network material, balanced out by surfactants and polymers, and arranged by reasonable strategies for medication conveyance applications, through different courses of organization. Plan approach is most reasonable with high log P esteem, high dissolving point, and high portion of medication. Nanosuspension has been accounted for not exclusively to improve ingestion and bioavailability which help to lessen the portion of ordinary oral definition. Medication molecule estimate decrease prompts an expansion in surface territory and thus disintegration. Moreover, an expansion in immersion solvency is proposed by molecule estimate decrease because of an expanded disintegration weight. An expanding measure of indistinct medication portion could initiate higher immersion solvency and medication is kept up in the required crystalline state with diminished molecule estimate, prompting an expanded disintegration rate, improved bioavailability.

**INTRODUCTION**

A nanosuspension is a submicron colloidal scattering of medication particles. A pharmaceutical nanosuspension is characterized as in all respects finely colloid, biphasic, scattered, and strong medication particles in a fluid vehicle, measure beneath 1  $\mu\text{m}$ , with no lattice material, balanced out by surfactants and polymers, and arranged by reasonable strategies for medication conveyance applications, through different courses of organization like oral, topical, parenteral, visual and aspiratory routes.<sup>[1,2]</sup> The molecule measure dissemination of the strong particles in nanosuspensions is generally short of what one micron with a normal molecule estimate going somewhere in the range of 200 and 600 nm.<sup>[3]</sup> A nanosuspension not just takes care of the issue of poor dissolvability and bioavailability yet additionally modifies the pharmacokinetics of medication and that improves sedate wellbeing and adequacy. In the event of medications that are insoluble in both water and in natural media as opposed to utilizing lipidic frameworks, nanosuspensions are utilized as a definition approach. Nanosuspension plan approach is most appropriate for the mixes with high log P esteem, high softening point, and high portion. The utilization of nanotechnology to plan inadequately water-dissolvable medications as nanosuspension offers the chance to address nature of the lack related with this class of medications. Nanosuspension has been accounted for to upgrade ingestion and bioavailability; it might diminish the

portion of the ordinary oral measurement shapes. Medication molecule estimate decrease prompts an expansion in surface region and thusly in the rate of disintegration as portrayed by the Nernst-Brunner and Levich change of the Noyes-Whitney condition. Also, an expansion in immersion dissolvability is proposed by molecule estimate decrease because of an expanded disintegration weight clarified by the Ostwald-Freundlich condition. An expanding measure of undefined medication division could incite higher immersion solvency. In nanosuspension innovation, the medication is kept up in the required crystalline state with diminished molecule measure, prompting an expanded disintegration rate and along these lines improved bioavailability. Medications exemplified inside nanosuspensions exist in pharmaceutically adequate crystalline or formless state. Nanosuspensions can effectively plan the block dust atoms for improved disintegration and great retention.

Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of  $10^{-9}$  or one billionth. Some comparisons of nanoscale are given below,  
0.1 nm = Diameter of one Hydrogen atom.  
2.5 nm = Width of a DNA molecule  
1 micron = 1000 nm.  
1 nm =  $10^{-9}\text{m}$  =  $10^{-7}\text{cm}$  =  $10^{-6}\text{mm}$ .  
Micron =  $10^{-6}\text{m}$  =  $10^{-4}\text{cm}$  =  $10^{-3}\text{mm}$ .

For a long span of time micronization of inadequately solvent medications by colloid factories or fly plants was liked. The general molecule measure appropriation ranges from 0.1 $\mu$ m to roughly 25 $\mu$ m, just unimportant sum being beneath 1 $\mu$ m in the nanometer range.<sup>[4]</sup>

Over 40% of medications are inadequately dissolvable in water, so they show issues in detailing them in regular dose shapes. Likewise, for class II drugs which are ineffectively dissolvable in watery and natural media, the issue is progressively mind boggling. Planning nanosuspension is favored for such aggravates that are insoluble in water (however are solvent in oil) with high log P esteem. Different ways to deal with determination issues of low dissolvability and low bioavailability micronization, co-dissolvability, slick arrangement, salt development some different methods are liposomes, emulsions, microemulsion, strong scattering,  $\beta$ -cyclodextrin consideration complex and so forth. Be that as it may, a significant number of these methods are not generally pertinent to all medications. In these cases nanosuspensions are liked. If there should arise an occurrence of medications that are insoluble in both water and in inorganic media as opposed to utilizing lipidic frameworks, nanosuspensions are utilized as a plan approach. It is most appropriate for the mixes with high log P esteem, high dissolving point, and high portion. Nanosuspensions can be utilized to upgrade the dissolvability of medications that are inadequately solvent in fluid just as lipid media. Thus, the rate of flooding of the dynamic compound increments and the greatest plasma level is achieved quicker (e.g., oral or intravenous (IV) organization of the nanosuspension). This is one of the one of a kind points of interest that it has over different methodologies for improving dissolvability. It is helpful for atoms with poor dissolvability, poor penetrability or both, which represents a critical test for the formulators.

Serious issues related with inadequately water-solvent compound.<sup>[5]</sup>

- Poor bioavailability.
- Inability to upgrade lead compound choice dependent on adequacy and wellbeing
- Fed/fasted variety in bioavailability
- Lack of portion reaction proportionality
- Suboptimal dosing
- Use of unforgiving excipients, i.e., extreme utilization of co-solvents and different excipients
- Use of outrageous fundamental or acidic conditions to upgrade solubilization.

Albeit, all advertised items, at present are delivered by purported 'top-down systems', in which the nanoparticles are acquired through size decrease into the submicron-extend, base up procedures and particularly controlled precipitation technique, are strategies for enthusiasm for nanozation of ineffectively solvent medications. In this technique, with no brutal conditions and just with basic types of gear one could diminish the molecule size to

couple of hundred nanometers go. In this way, whatever strategy which is utilized for the generation of nanosuspension, a cautious assessment of the sort and centralization of the stabilizer is a basic stage for the fruitful creation of nanosuspension. Both polymeric and surfactant stabilizers can be utilized for this purpose. Nanosuspensions vary from Nanoparticles, which are polymeric colloidal bearers of medications (Nanospheres and nanocapsules), and from strong lipid nanoparticles (SLN), which are lipidic transporters of medication. The key contrast from customary definitions of suspensions is that the molecule estimate dispersion of the strong particles in nanosuspensions is generally under 1  $\mu$ m (for example 0.1nm-1000nm), with a normal molecule measure go between 200– 600 nm. Then again, the molecule distance across required in most great pharmaceutical suspensions, is 1 to 50  $\mu$ m. In nanosuspensions, the general bioavailability is improved by an expansion in surface region and immersion dissolvability through molecule measure decrease. This framework can't be accomplished by the regular processing techniques.<sup>[6]</sup>

### Classification of nanosuspension<sup>[7]</sup>

#### I. Based On General Classes

- Oral suspension
- Externally applied suspension
- Parenteral suspension

#### II. Based On Proportion of Solid Particles

- Dilute suspension (2 to 10% w/v solid)
- Concentrated suspension (50% w/v solid)

#### III. Based On Electrokinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension

#### IV. Based On Size Of Solid Particles

- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 ng)

### Advantages of Nanosuspension

1. Increase in the disintegration speed and immersion solvency of the medication
2. Improved natural execution
3. Ease of assembling and scale-up
4. Long-term physical security
5. Versatility
6. Increase in the oral assimilation
7. Improved portion proportionality.
8. Its general pertinence to most medications and effortlessness
9. It can be connected for ineffectively water solvent medications.
10. It can be given by any course.
11. Reduced tissue disturbance if there should arise an occurrence of subcutaneous/intramuscular organization.

12. Rapid disintegration and tissue focusing on can be accomplished by IV course of organization.
13. Oral organization of nanosuspension give quick beginning, decreased bolstered/fasted proportion and improved bioavailability.
14. The ingestion structure assimilation window can be expanded, because of decrease in the molecule measure.
15. Higher bioavailability and increasingly steady dosing if there should arise an occurrence of visual organization and inward breath conveyance.
16. Drug with higher log P esteem can be detailed as nanaosuspensions to expand the bioavailability of such medications.
17. Improvement in organic execution because of high disintegration rate and immersion dissolvability of the medications.
18. Nanosuspensions can be consolidated in tablets, pellets, hydrogel and suppositories are appropriate for different courses of organization.
19. Increasing the shapeless portion in the particles prompting a potential change in the crystalline structure and higher solvency.
20. Possibility of surface-change of nanosuspension for site explicit conveyance.
21. Possibility of enormous scale generation, the essential for the acquaintance of conveyance framework with the market.

#### Disadvantage of Nanosuspension<sup>[8]</sup>

1. Physical dependability, sedimentation and compaction can cause issues.
2. It is massive adequate consideration must be taken amid taking care of and transport.
3. Improper portion.
4. Uniform and exact portion can't be accomplished

#### General Features of Nanosuspension

- It can be connected for the inadequately water dissolvable medications.
- Rapid disintegration and tissue focusing on can be accomplished by IV course of organization.
- Oral organization of nanosuspensions give quick and improved bioavailability.
- Long-term physical dependability because of the nearness of stabilizers.
- Nanosuspensions can be fused in tablets, pellets, hydrogels.

#### Preparation of Nanosuspension

##### 1. Physical Long-term stability

Extraordinary element of nanosuspensions is the nonappearance of Ostwald aging, which is suggestive of their long haul physical solidness. Ostwald aging is in charge of precious stone development and in this way arrangement of microparticles. Ostwald aging is brought about by the distinctions in disintegration weight/immersion dissolvability among little and huge particles. Atoms diffuse from the most noteworthy concentrated zone around little particles (higher

immersion dissolvability) to regions around bigger particles having a lower tranquilize focus. This prompts the development of a supersaturated arrangement around the huge particles and thusly to medicate crystallization and development of the enormous particles. The dispersion procedure of the medication from little particles to the enormous particles leaves a territory around the little particles that isn't soaked any more, thus prompting disintegration of the medication from the little particles lastly finishes vanishing of the little particles.

#### 2. Internal structure of Nanosuspensions

The high-vitality contribution amid breaking down procedure causes auxiliary changes inside the medication particles. At the point when the medication particles are presented to high-weight homogenization, particles are changed from crystalline state to formless state. The adjustment in state relies on the hardness of medication, number of homogenization cycles synthetic nature of medication and power thickness connected by homogenizer.

#### 3. Adhesiveness

There is an unmistakable increment in adhesiveness of ultra-fine powders contrasted with coarse powders. This adhesiveness of little medication nanoparticles can be abused for improved oral conveyance of ineffectively dissolvable medications. A definitely amazing report is that of the expansion in bioavailability for danazol from 5 % (as macrosuspension) to 82% (as nanosuspension).

#### 4. Crystalline state and morphology

A potential change in the crystalline structure of nanosuspensions saying expanding the indistinct division in the molecule or notwithstanding making totally shapeless particles is a normal for thought. The utilization of high weights amid the creation of nanosuspensions was found to advance the shapeless state.

#### 5. Increase in Saturation Solubility and Dissolution Velocity of medication

Disintegration of medication is expanded because of increment in the surface region of the medication particles from micrometers to the nanometer measure. As per Noyes-Whitney condition (Equation no.1), disintegration speed increments because of increment in the surface zone from micron size to particles of nanometer measure.

$$dx/dt = [(D \times A)/h] [Cs - X/V] - \text{Equation (1)}$$

Where D is dispersion coefficient, An is surface region of molecule, dx/dt is the disintegration speed, V is volume of disintegration medium and, h is the thickness of the dissemination layer and X is the fixation in encompassing fluid.

#### Benefits of Nanosuspension<sup>[1,2,9-11]</sup>

1. Reduced molecule estimate, expanded medication disintegration rate, expanded rate and degree of

ingestion, expanded bioavailability of medication, region under plasma versus time bend, beginning time, top medication level, diminished inconstancy, and decreased encouraged/fasted impacts. Because of the molecule estimate decrease, the infiltration ability of topical nanosuspension arrangements increments essentially.

2. Nanosuspensions can be utilized for exacerbates that are water insoluble yet which are solvent in oil. Then again, nanosuspensions can be utilized conversely with lipidic frameworks, and effectively detail intensifies that are insoluble in both water and oils.
3. Nanoparticles can stick to the gastrointestinal mucosa, dragging out the contact time of the medication and along these lines improving its assimilation.
4. A articulated favorable position of nanosuspension is that there are numerous organization courses for nanosuspensions, for example, oral, parenteral, pneumonic, dermal and visual.
5. Nanosuspension of nanoparticles (NPs) offers different focal points over ordinary visual measurement shapes, incorporating decrease in the measure of portion, support of medication discharge over a drawn out timeframe, decrease in foundational poisonous quality of medication, improved medication assimilation because of longer home time of nanoparticles on the corneal surface, higher medication focuses in the contaminated tissue, and reasonableness for ineffectively water-dissolvable medications, and littler particles are preferred endured by patients over bigger particles; in this way, nanoparticles may speak to promising medication bearers for ophthalmic applications.
6. Nanosuspension has low frequency of reactions by the excipients.
7. Nanosuspensions beat conveyance issues for the mixes by blocking the need to break up them and by keeping up the medication in a favored crystalline condition of size adequately little for pharmaceutical worthiness.
8. Increased protection from hydrolysis and oxidation and expanded physical security to settling.
9. Reduced organization volumes, basic for intramuscular, subcutaneous, and ophthalmic use.
10. Finally, nanosuspensions can give the aloof focusing on.

#### Preparation methods of Nanosuspension

There are different methods of Nanosuspensions preparation

- Homogenization in water (DissoCubes).
- Media processing (Nanocrystal or NanoSystems).
- Homogenization in non-watery media (Nanopure).
- Combined precipitation and homogenization (Nanoedge).
- Nanojet innovation
- Emulsification-dissolvable dissipation procedure.

- Hydrosol strategy
- Supercritical liquid strategy.
- Dry co-granulating
- Emulsion as layout
- Microemulsion as template<sup>[8]</sup>

Chiefly there are two strategies for planning of Nanosuspensions. The regular techniques for precipitation (Hydrosols) are called 'Base up innovation'. The 'Top Down Technologies' are the breaking down strategies are favored over the precipitation techniques. The 'Top Down Technologies' incorporate Media Milling (Nanocrystals), High Pressure Homogenization in water (DissoCubes), High Pressure Homogenization in non watery media (Nanopure) and mix of Precipitation and High-Pressure Homogenization (Nanoedge).

#### 1) Bottom-up innovation

#### 2) Top-down technology<sup>[4,12-18]</sup>

The expression "Base up innovation" implies that one begins from the sub-atomic dimension, and goes by means of sub-atomic relationship to the arrangement of a strong molecule. That implies that we are talking about traditional precipitation methods by decreasing the dissolvable quality, for instance, by emptying the dissolvable into a nonsolvent or changing the temperature or a blend of both. Precipitation is a traditional method in pharmaceutical science and technology.<sup>[19-23]</sup>

#### Points of interest

- 1) Use of basic and minimal effort gear.
- 2) Higher immersion solvency is the favorable position for precipitation contrasted with different strategies for Nanosuspension arrangement.

#### Drawbacks

- 1) The medication should be dissolvable in any event one dissolvable (in this way barring every new medication that are at the same time ineffectively solvent in fluid and in natural media).
- 2) The dissolvable should be miscible with in any event one nonsolvent.
- 3) Solvent deposits should be evacuated, subsequently expanding creation costs.
- 4) It is an little bit dubious to protect the molecule character (for example measure, particularly the formless portion). When all is said in done, it is suggested that a second sequential procedure must be performed for molecule protection that is splash drying or lyophilization.<sup>[24-26]</sup>

#### Top-Down Technology

The top down advances incorporate

- a) Media processing
- b) High weight homogenization

#### a) Media Milling

Nanosuspensions are created by utilizing high-shear media plants or pearl factories. The factory comprises of

a processing chamber, processing shaft and a distribution chamber. A fluid suspension of the medication is then bolstered into the plant containing little crushing balls/pearls. As these balls pivot at a high shear rate under controlled temperature, they fly through the pounding container inside and sway against the example on the contrary granulating container divider. The consolidated powers of contact and effect produce a high level of molecule estimate decrease. The processing media or balls are made of clay sintered aluminum oxide or zirconium oxide or exceedingly cross-connected polystyrene tar with high scraped spot obstruction. A planetary ball factory (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) is one case of hardware that can be utilized to accomplish a crush measure underneath 0.1  $\mu\text{m}$ . A Nanosuspension of Zn-Insulin with a mean molecule size of 150 nm was readied utilizing the wet processing system.

#### Points of interest

1. Straightforward innovation
2. Minimal effort process in regards to the processing itself
3. Enormous scale creation conceivable somewhat (group process).

#### Drawbacks

1. Potential disintegration from the processing material prompting item tainting.
2. Span of the procedure not being very generation amicable.
3. Potential development of germs in the water stage when processing for quite a while.
4. Time and expenses related with the detachment system of the processing material from the medication nanoparticle suspension, particularly while delivering parenteral clean products.<sup>[27-30]</sup>

#### High Pressure Homogenisation

##### Disso blocks

Disso blocks are designed utilizing cylinder hole type high weight homogenizers. High weight homogenization has been utilized to plan nanosuspension of numerous ineffectively water dissolvable medications. Homogenization includes the constraining of the suspension under strain through a valve having a restricted gap. The instrument can be worked at weight changing from 100-1500 bars and up to 2000 bars with volume limit of 40ml.

The worry with this strategy is the requirement for little example particles before stacking and the way that numerous cycles of homonization are required. Before exposing the medication to the homogenization procedure, it is fundamental to shape a pre-suspension of the microsized sedate in a surfactant arrangement utilizing fast stirrer. During the homogenization procedure, the medication suspension is squeezed through the homogenization hole so as to accomplish nanosizing of the medication. In cylinder hole

homogenizer, molecule estimate decrease depends on the cavitation rule.

A cylinder hole homogenizer like APV Gaulin type has been appeared. Particles are likewise decreased because of high shear powers and the crash of the particles against one another. The scattering contained in 3cm measurement barrel, all of a sudden goes through an extremely thin hole of 25 $\mu\text{m}$ . The decrease in distance across of 3cm to 25 $\mu\text{m}$  prompts increment in powerful weight and lessening of static weight beneath the breaking point of water at room temperature. Because of this water begins bubbling at room temperature and structures bubbles, which implode when the suspension leaves the hole and ordinary pneumatic force, are reached.<sup>[31]</sup>

#### Nanopure

Nanopure is suspensions homogenized in without water media or water blends. In the Dissocubes innovation, the cavitation is the deciding component of the procedure. In any case, rather than water, oils and sleek unsaturated fats have extremely low vapor weight and a high breaking point. Subsequently, the drop of static weight won't be sufficiently adequate to start cavitation. Licenses covering deterioration of polymeric material by high-weight homogenization notice that higher temperatures of about 80 $^{\circ}\text{C}$  advanced breaking down, which can't be utilized for thermolabile mixes. In nanopure innovation, the medication suspensions in the non-watery media were homogenized at 0 $^{\circ}\text{C}$  or even underneath the point of solidification and henceforth are classified "profound stop" homogenization. The outcomes acquired were practically identical to Dissocubes and subsequently can be utilized adequately for thermolabile substances at milder conditions.<sup>[27,32]</sup>

#### Nanoedge

The essential standards of Nanoedge are equivalent to that of precipitation and homogenization. blend of these procedures results in littler molecule size and better soundness in a shorter time. The significant disadvantage of the precipitation system, for example, precious stone development and long term security, can be settled utilizing the Nanoedge innovation. In this procedure, the accelerated suspension is additionally homogenized; prompting decrease in molecule measure and staying away from precious stone development. Precipitation is performed in water utilizing water-miscible solvents, for example, methanol, ethanol and isopropanol. It is attractive to expel those solvents totally, in spite of the fact that they can be endured to a limited degree in the definition. For a powerful creation of Nanosuspensions utilizing the Nanoedge innovation, a vanishing step can be incorporated to give a dissolvable free adjusted beginning material pursued by high-weight homogenization.<sup>[33]</sup>

### Emulsion Diffusion Method

Aside from the utilization of emulsion as medication conveying vehicle they can likewise be utilized as layouts to create Nanosuspension. The utilization of emulsions as layouts is material for those medications that are dissolvable in either unstable natural dissolvable or incompletely water-miscible solvent. Such solvents can be utilized as the scattered period of the emulsion. A natural dissolvable or blend of solvents stacked with the medication is scattered in the watery stage containing appropriate surfactants with mixing to shape an emulsion. The got emulsion was additionally homogenized by high weight homogenization. After homogenization cycles the emulsion was weakened with water, homogenized by homogenizer to diffuse the natural dissolvable and convert the beads into strong particles. Since one molecule is framed in every emulsion bead, it is conceivable to control the molecule size of the Nanosuspension by controlling the extent of the emulsion advancing the surfactant piece expands the admission of natural stage and eventually the medication stacking in the emulsion. Initially methanol, ethanol, ethyl acetic acid derivation chloroform are utilized as a natural solvents.<sup>[4,34-35]</sup>

### Advantages

- Use of specific gear isn't important.
- Particle size can without much of a stretch be constrained by controlling the span of the emulsion bead.
- Ease of scale-up if plan is streamlined appropriately.

### Weaknesses

- Drugs that are ineffectively solvent in both fluid and natural media can't be defined by this procedure.
- Safety concerns in view of the utilization of unsafe solvents all the while.
- Need for diultrafiltration for cleansing of the medication Nanosuspension, which may render the procedure expensive.
- High measure of surfactant/stabilizer is required when contrasted with the generation strategies portrayed before.

### Smaller scale emulsion Template<sup>[36]</sup>

This procedure pursues a natural dissolvable or blend dissolvable stacked with the medication scattered in a fluid stage containing appropriate surfactants to shape an emulsion. The natural stage is then dissipated under decreased strain to make tranquilize particles encourage immediately to frame the Nanosuspension which is balanced out by surfactants. Another strategy utilizes incompletely water-miscible solvents, for example, butyl lactate, benzyl liquor and triacetin as the scattered stage rather than unsafe solvents.

### Focal points

- Use of particular hardware isn't vital.

- Particle size can undoubtedly be constrained by controlling the measure of the emulsion bead.
- Ease of scale-up if detailing is upgraded appropriately.

### Hindrances

- Drugs that are ineffectively dissolvable in both fluid and natural media can't be figured by this procedure.
- Need for diultrafiltration for refinement of the medication Nanosuspension, which may render the procedure expensive.
- High measure of surfactant/stabilizer is required when contrasted with the generation procedures portrayed before.

### Supercritical Fluid Method<sup>36</sup>

Supercritical liquid innovation can be utilized to create nanoparticles from medication arrangements. The different techniques endeavored are quick development of supercritical arrangement process (RESS), supercritical enemy of dissolvable procedure and precipitation with compacted hostile to dissolvable procedure (PCA). The RESS includes extension of the medication arrangement in supercritical liquid through a spout, which prompts loss of dissolvable intensity of the supercritical liquid bringing about precipitation of the medication as fine particles. Youthful et al arranged cyclosporine nanoparticles in the size scope of 400-700 nm utilizing this procedure. In the PCA technique, the medication arrangement is atomized into a chamber containing packed CO<sub>2</sub>. As the dissolvable is expelled, the arrangement gets supersaturated and in this manner accelerates as fine gems. The supercritical enemy of dissolvable procedure utilizes a supercritical liquid where a medication is inadequately solvent and a dissolvable for the medication that is additionally miscible with the supercritical liquid. The medication arrangement is infused into the supercritical liquid and the dissolvable gets extricated by the supercritical liquid and the medication arrangement gets supersaturated. The medication is then hastened as fine gems.

### Weaknesses

- Use of unsafe solvents and utilization of high extents of surfactants and stabilizers as contrasted and different procedures,
- Particle nucleation abundance because of transient high super immersion, which may likewise result in the advancement of an indistinct structure or another undesired polymorph.

### Soften emulsification method<sup>[35,36]</sup>

In this technique sedate is scattered in the watery arrangement of stabilizer and warmed over the dissolving purpose of the medication and homogenized to give an emulsion. Amid this procedure, the example holder was enwrapped with a warming tape fitted with temperature controller and the temperature of emulsion was kept up over the liquefying purpose of the medication. The

emulsion was then chilled off either gradually to room temperature or on an icebath.

### Bit of leeway

Liquefy emulsification system with respect to the dissolvable dissemination technique is all out shirking of natural solvents amid the generation procedure.

### Dry Co-Grinding<sup>[37]</sup>

As of late, Nanosuspensions can be gotten by dry processing systems. Effective work in planning stable Nanosuspensions utilizing dry-crushing of inadequately solvent medications with dissolvable polymers and copolymers in the wake of scattering in a fluid media has been accounted for. Numerous solvent polymers and copolymers, for example, PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin subsidiaries have been utilized.

### Formulation Consideration

#### Stabilizer

Stabilizer assumes a significant job in the definition of nanosuspensions. Without a suitable stabilizer, the high surface vitality of nanosized particles can instigate agglomeration or conglomeration of the medication gems. The fundamental elements of a stabilizer are to wet the medication particles completely, and to avoid Ostwald's ripening<sup>[38,39]</sup>, and agglomeration of nanosuspensions so as to yield a physically steady definition by giving steric or ionic obstructions. The sort and measure of stabilizer pronouncedly affects the physical dependability and in-vivo conduct of nanosuspensions. Now and again, a blend of stabilizers is required to get a steady nanosuspension. The medication to-stabilizer proportion in the plan may differ from 1:20 to 20:1 and ought to be researched for a particular case. Stabilizers that have been investigated so far incorporate cellulose, poloxamers, polysorbates, lecithins and povidones. Lecithin is the stabilizer of decision on the off chance that one plans to build up a parenterally satisfactory and autoclavable nanosuspension.

#### Natural solvents

Natural solvents might be required in the plan of nanosuspensions on the off chance that they are to be readied utilizing an emulsion or microemulsion as a layout. As these strategies are still in their earliest stages, expand data on definition contemplations isn't accessible. The adequacy of the natural solvents in the pharmaceutical field, their poisonous quality potential and the simplicity of their expulsion from the plan should be viewed as while planning nanosuspensions utilizing emulsions or microemulsions as formats. The pharmaceutically satisfactory and less dangerous water-miscible solvents, for example, ethanol and isopropanol, and incompletely water-miscible solvents, for example, ethyl acetic acid derivation, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl liquor, are favored in the definition over the regular unsafe solvents, for example, dichloromethane. Furthermore, mostly

water-miscible natural solvents can be utilized as the inner period of the microemulsion when the nanosuspensions are to be delivered utilizing a microemulsion as a format.

### Co-surfactants

The decision of co-surfactant is basic when utilizing microemulsions to detail nanosuspensions. Since co-surfactants can extraordinarily impact stage conduct, the impact of co-surfactant on take-up of the inward stage for chosen microemulsion arrangement and on medication stacking ought to be researched. In spite of the fact that the writing portrays the utilization of bile salts and dipotassium glycerhizinate as co-surfactants, different solubilizers, for example, Transcutol, glycofurol, ethanol and isopropanol, can be securely utilized as co-surfactants in the plan of microemulsions.

### Different added substances

Nanosuspensions may contain added substances, for example, supports, salts, polyols, osmogent and cryoprotectant, contingent upon either the course of organization or the properties of the medication moiety.<sup>[40]</sup>

### Portrayal of Nanosuspension<sup>[7,15-19,41-44]</sup>

#### In-vitro assessments

Shading, Odor, Taste. These attributes are particularly significant in orally administered definition. Varieties in taste, particularly of dynamic constituents, can offered be credited to changes in molecule measure, gem propensity and resulting molecule disintegration.

Changes in shading, smell and taste can likewise demonstrate substance flimsiness.

### Molecule Size Distribution

**Molecule estimate conveyance** decides the physiochemical conduct of the plan, for example, immersion dissolvability, disintegration speed, physical strength, and so forth. The molecule estimate appropriation can be dictated by photon connection spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS technique can quantify particles in the size scope of 3 nm to 3 $\mu$ m and the LD strategy has an estimating scope of 0.05-80 $\mu$ m. The coulter counter multisizer gives irrefutably the quantity of particles, rather than the LD technique, which gives just a relative size dispersion. For IV use, particles ought to be under 5 $\mu$ m, taking into account that the littlest size of the vessels is 5-6  $\mu$ m and thus a higher molecule size can prompt fine bar and embolism.

**Zeta Potential** Zeta potential means that the soundness of the suspension. For a steady suspension balanced out just by electrostatic shock, a base zeta capability of  $\pm 30$ mV is required while if there should arise an occurrence of a joined electrostatic and steric stabilizer, a zeta capability of  $\pm 20$  mV would be adequate.

**Gem Morphology** To portray the polymorphic changes because of the effect of high-weight homogenization in the crystalline structure of the medication, strategies like X-beam diffraction investigation in blend with differential checking calorimetry or differential warm examination can be used. Nanosuspensions can experience an adjustment in the crystalline structure, which might be to a nebulous structure or to other polymorphic structures due to high-weight homogenization.

#### **Disintegration Velocity and Saturation Solubility**

Nanosuspensions have a significant favorable position over different procedures, that it can build the disintegration speed just as the immersion solvency. These two parameters ought to be resolved in different physiological arrangements. The appraisal of immersion dissolvability and disintegration speed helps in deciding the in vitro conduct of the plan. Bohm et al. detailed an expansion in the disintegration weight just as disintegration speed with a decrease in the molecule size to the nanometer go. Estimate decrease prompts an expansion in the disintegration weight.

**Thickness** Specific gravity or thickness of the detailing is a significant parameter. An abatement in thickness frequently shows the nearness of ensnared air inside the structure of the detailing. Thickness estimations at a given temperature ought to be made utilizing very much blended, uniform definition; accuracy hydrometer encourage such estimations.

#### **pH Value**

The pH estimation of watery detailing ought to be taken at a given temperature and simply in the wake of settling harmony has been come to, to limit "pH float" and terminal surface covering with suspended particles. Electrolyte ought not be added to the outer period of the detailing to balanced out the pH.

**Bead Size** The drop estimate dispersion of miniaturized scale emulsion vesicles can be dictated by either light dissipating strategy or electron microscopy. Dynamic light dissipating spectrophotometer which utilizes a neon laser of wavelength 632 nm.

#### **Thickness Measurement**

The thickness of lipid based definitions of a few organizations can be estimated at various shear rates at various temperatures utilizing Brookfield type rotating viscometer. The example room of the instrument must be kept up at 37°C by a thermo shower and the examples, for the estimation are to be inundated in it.

**Soundness of Nanosuspension** The high surface vitality of nanosized particles actuates agglomeration of the medication precious stones. The fundamental capacity of the stabilizer is to wet the medication particles altogether to counteract Ostwald aging and agglomeration of the Nanosuspension and structure a physically steady

definition by giving a steric or an ionic hindrance. Run of the mill instances of stabilizers utilized in Nanosuspensions are cellulose, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin might be favored in creating parenteral Nanosuspension.

**In-Vivo Biological Performance** The foundation of an in-vitro/in-vivo relationship and the observing of the in-vivo execution of the medication is a fundamental piece of the examination, regardless of the course and the conveyance framework utilized. It is absolutely critical on account of intravenously infused. Nanosuspensions since the in-vivo conduct of the medication relies upon the organ circulation, which thusly relies upon its surface properties, for example, surface hydrophobicity and associations with plasma proteins indeed, the subjective and quantitative organization of the protein ingestion design saw after the intravenous infusion of nanoparticles is perceived as the basic factor for organ conveyance. Subsequently, reasonable procedures must be utilized so as to assess the surface properties and protein cooperations to get a thought of in vivo conduct. Procedures, for example, hydrophobic connection chromatography can be utilized to decide surface hydrophobicity, while 2-D PAGE can be utilized for the quantitative and subjective estimation of protein adsorption after intravenous infusion of medication nanosuspensions in creatures.

#### **Major Challenges**<sup>[45-47]</sup>

- Although nanoemulsion and nanosuspension give incredible favorable circumstances as a conveyance framework, anyway they languish over some real difficulties and constraints which incorporate.
- Although nanoemulsion and nanosuspension give extraordinary focal points as a conveyance framework, anyway they languish over some significant difficulties and constraints which incorporate
- The detailing of nanoemulsion is a costly procedure because of size decrease of beads is troublesome as it required an uncommon sort of instruments and procedure techniques.
- For precedent, homogenizer (instrument required for the nanoemulsions definition) game plan is a costly procedure. All the more ever miniaturized scale fluidization and ultrasonication (fabricating process) need enormous measure of money related help.
- One issue related with nanoemulsion is their strength. Despite the fact that it is commonly acknowledged that these frameworks could stay stable even by years, nonetheless, because of the little bead estimate, it has been accounted for that the Oswald maturing could harm nanoemulsions and nanosuspensions, making their application be constrained. Thusly, much of the time, nanoemulsions and nanosuspensions are required to be arranged in no time before their utilization.

- Use of an enormous centralization of surfactant and cosurfactant fundamental for balancing out the nano beads.
- Limited solvency limit with regards to high dissolving substances.
- Nanoemulsion security is impacted by natural parameters, for example, temperature and pH.
- Lack of comprehension of the instrument of generation of submicron beads and the job of surfactants and cosurfactants.
- Lack of showing of the advantages that can be acquired from utilizing nanoemulsions when contrasted and the established macroemulsion and macrosuspension frameworks.
- Lack of comprehension of the interfacial science that is engaged with generation of nanoemulsions and nanosuspension.

### Contextual analyses

#### Case 1<sup>[18,48,49]</sup>

Polymeric nanosuspensions were set up from Eudragit RS100 and RL100 polymer tars and stacked with Flurbiprofen (FLU), with the go for improving the accessibility of the medication at an intra-visual dimension for the counteractive action of the miosis instigated amid extracapsular waterfall medical procedure. Nanosuspensions were set up by a semi emulsion dissolvable dispersion procedure utilizing diverse definition parameters (medication to polymer proportion, beginning polymer fixation, fomentation speed, and so forth.). The subsequent nanoparticles indicated mean sizes around 100 nm. The medication was fused with exceptionally significant returns in the polymer grids. One plan was tried in the rabbit contrasted with a business eye-drop item containing a proportionate measure of FLU sodium salt. The joining of the medication in the polymer framework upgraded FLU offending action against the miosis initiated by a careful injury to the eye foremost chamber and expanded its dynamic focus in the watery amusingness. For the likelihood of regulating the planning conditions and the dependability appeared upon capacity, as the first suspensions or after stop drying, just as for the excellent passableness, the portrayed details might be valuable in clinical practice to keep up mydriasis amid waterfall or other eye careful medications.

#### Case 2

Paclitaxel is a diterpenoid separated from *Taxus brevifolia*. It is compelling for different malignant growths, particularly ovarian and bosom disease. Because of its fluid insolubility, it is managed broken down in ethanol and Cremophor® EL (BASF, Ludwigshafen, Germany), which can cause genuine unfavorably susceptible responses. So as to take out Cremophor® EL, Paclitaxel was figured as a nanosuspension by high-weight homogenization. The nanosuspension was lyophilized to acquire the dry Paclitaxel nanoparticles (normal size,  $214.4 \pm 15.03$  nm), which improved both the physical and synthetic strength

of Paclitaxel nanoparticles. Paclitaxel disintegration was additionally improved by the nanosuspension. The pharmacokinetics and tissue appropriation of Paclitaxel were analyzed after intravenous organization of Paclitaxel nanosuspension and Paclitaxel infusion. Paclitaxel infusion indicated decreased zone under the fixation, more prominent leeway, and shorter disposal half-life contrasted and the Paclitaxel arrangement, while interestingly, the Paclitaxel nanosuspension brought about a fundamentally more noteworthy AUC<sub>0-∞</sub> in liver, lung, and spleen, yet not in heart or kidney.

#### Case 350

Omeprazole is a proton siphon inhibitor, which is utilized for the treatment of peptic ulcers, reflux esophagitis and Zollinger-Ellison disorder. It is an inadequately dissolvable, synthetically labile medication with a high corruption rate in fluid media. Obviously, to yield an intravenously injectable item, a nanosuspension as opposed to a macrosuspension should be delivered. The likelihood of shielding Omeprazole from corruption by utilizing the Disso Cubes method was researched. This system is reasonable for delivering particulate medication definitions so as to shield synthetic labile medications from corruption. The medication nanosuspensions are anything but difficult to deliver and, show magnificent substance strength contrasted with medication arrangements. It is conceivable to deliver very focused nanosuspensions, which are synthetically steady and shielded from debasement. The superior fluid chromatography examination has demonstrated the transcendence of the nanosuspension delivered by high weight homogenization in contrast with a watery arrangement. Indeed, even multi month after generation no staining or medication misfortune was conspicuous when the nanosuspension was delivered at 8° C. Accordingly it very well may be expressed that the generation of nanosuspensions by high weight homogenization is appropriate for avoiding corruption of labile medications.

#### Uses of Nanosuspension

Uses of nanosuspensions had landmarking history. Among these couple of utilizations are given beneath.

#### Oral Drug Delivery

More often than not the oral course is favored in light of the fact that it has various surely understood advantages. Some orally controlled anti-toxins, for example, atovaquone and Buparvaquone mirror this issue great. Nanosizing of such medications can prompt an emotional increment in their oral ingestion and in this way bioavailability. The oral organization of naproxen nanoparticles lead to a region under the bend (AUC) (0–24 h) of 97.5mg-h/L contrasted and simply 44.7mg-h/L for naprosyn suspensions and 32.7mg-h/L for anaprox tablets. Oral organization of the gonadotropin inhibitor Danazol as a nanosuspension prompts an outright bioavailability of 82.3 and the traditional scattering (Danocrine) just to 5.2%. Ananosuspension of

amphotericin B demonstrated a noteworthy improvement in its oral assimilation in correlation with the regular business formulation.<sup>[2]</sup>

### Bioavailability Enhancement

The poor oral bioavailability of the medication might be because of poor solvency, poor penetrability, or poor steadiness in the gastrointestinal tract (GIT). Nanosuspensions settle the issue of poor bioavailability by taking care of the twin issues of poor solvency and poor porousness over the film. Bioavailability of ineffectively dissolvable oleanolic corrosive, a hepatoprotective operator, was improved utilizing a nanosuspension definition. The helpful impact was essentially improved, which demonstrates higher bioavailability. This was because of the quicker disintegration (90% in 20 min) of the lyophilized nanosuspension powder when contrasted and the disintegration from a coarse powder measure underneath 5  $\mu\text{m}$  to evade narrow blockage. What's more, nanosuspensions have been found to expand the adequacy of parenterally directed medications. Paclitaxel nanosuspensions uncovered their prevalence over taxol in diminishing the middle tumor burden.<sup>[51]</sup> So also, aphidicolin, an inadequately water solvent new enemy of parasitic lead particle, when controlled as a nanosuspension brought about an improvement in EC50 in contrast with DMSO-broke down drug.<sup>[52]</sup> Clofazimine nanosuspension, an ineffectively water-solvent antileprotic medicate, uncovered an improvement in security and adequacy over the liposomal clofazimine in *M. avium*-tainted femalemice.<sup>[53]</sup> Rainbow and collaborators detailed an intravenous itraconazole nanosuspension upgraded adequacy of antifungal movement in respect to an answer plan in rats.<sup>[54]</sup> Intrathecal conveyance of nanosuspension busulfan to a mouse model of neoplastic meningitis prompted a huge increment in survival.<sup>[9]</sup>

### Aspiratory Drug Delivery

Nanosuspensions may demonstrate to be a perfect methodology for conveying drugs that show poor dissolvability in aspiratory emissions. Watery nanosuspensions can be nebulized utilizing mechanical or ultrasonic nebulizers for lung conveyance. In view of their little size, almost certainly, in every vaporized bead at any rate one medication molecule is contained, prompting a progressively uniform appropriation of the medication in lungs. The nanoparticulate idea of the medication permits the fast dissemination and disintegration of the medication at the site of activity. In the meantime, the expanded adhesiveness of the medication to mucosal surfaces offers a drawn out habitation time for the medication at the retention site. This capacity of nanosuspensions offers fast beginning of activity at first, and after that controlled arrival of the dynamic moiety is profoundly advantageous and is required by most pneumonic maladies. Budesonide tranquilize nanoparticles were effectively nebulized utilizing a ultrasonic nebulizer.<sup>[2]</sup>

### Parenteral Drug Delivery

Nanosuspensions can be controlled by means of various parenteral organization courses running from intra-articular through Intraperitoneal to intravenous infusion. For organization by the parenteral course the medication either must be solubilized or has molecule/globule estimate underneath 5  $\mu\text{m}$  to stay away from hairlike blockage. Likewise, nanosuspensions have been found to build the viability of parenterally controlled medications. Paclitaxel nanosuspensions uncovered their prevalence over taxol in diminishing the middle tumor trouble. Thus, aphidicolin, an inadequately water solvent new enemy of parasitic lead particle, when regulated as a nanosuspension brought about an improvement in EC50 in contrast with DMSO-disintegrated tranquilize. Clofazimine nanosuspension, an inadequately water-dissolvable antileprotic sedate, uncovered an improvement in dependability and viability over the liposomal clofazimine in *M. avium*-contaminated femalemice. Rainbow and colleagues detailed an intravenous itraconazole nanosuspension upgraded adequacy of antifungal action in respect to an answer definition in rodents. Intrathecal conveyance of nanosuspension busulfan to a mouse model of neoplastic meningitis prompted a critical increment in survival.

### Visual Drug Delivery

Nanosuspensions can demonstrate to be an aid for medications that show poor dissolvability in lachrymal fluids.<sup>[2]</sup> The defensive boundaries of the eye make tranquilize conveyance troublesome without tissue harm. Poor medication assimilation and infiltration of medications to intraocular tissues limit the conveyance of medications. Utilization of nanoparticles and nanosuspensions for medication conveyance to the intraocular tissues is being created. One precedent is cross-connected polymer nanosuspensions of dexamethasone, which show improved calming action in a model of rabbit eye irritation.<sup>[55]</sup>

### Directed Drug Delivery

Nanosuspensions can be utilized for focused conveyance as their surface properties and in vivo conduct can without much of a stretch be modified by changing either the stabilizer or the milieu. The building of stealth nanosuspensions (closely resembling stealth liposomes) by utilizing different surface coatings for dynamic or detached focusing of the ideal site is the fate of focused medication conveyance systems<sup>56</sup>. Kayser planned a nanosuspension of aphidicolin to improve medicate focusing against Leishmania-Infected macrophages. He expressed that the medication in the ordinary structure had a compelling fixation (EC 50) of 0.16mcg/mL, though the nanosuspension definition had an improved action with an (EC 50) of 0.003mcg/mL.<sup>[57]</sup> Scholer et al. demonstrated an improved medication focusing to the cerebrum in the treatment of toxoplasmic encephalitis in another murine model contaminated with *Toxoplasma gondii* utilizing a nanosuspension detailing of atovaquone.<sup>[58]</sup>

### Mucoadhesion of the Nanoparticles

Nanoparticles orally directed as a suspension diffuse into the fluid media and quickly experience the mucosal surface. The immediate contact of the particles with the intestinal cells through a bioadhesive stage is the initial step before molecule ingestion. The adhesiveness of the nanosuspensions improves bioavailability as well as improves focusing of the parasites continuing in the GIT, for instance, *Cryptosporidium parvum*. Mucoadhesive Buparvaquone nanosuspensions, as a result of their delayed habitation at the contamination site, uncovered a 10-crease decrease in the infectivity score of *Cryptosporidium parvum* contrasted with the Buparvaquone nanosuspensions without mucoadhesive polymers.<sup>[2]</sup>

### Nanosuspension: Breaking the Barrier of the Skin

Medication nanoparticles can be consolidated into creams sans and water balms. The nanocrystalline structure prompts an expanded immersion dissolvability of the medication in the topical measurements structure and along these lines upgrading the dissemination of the medication into the skin.

### Focal Nervous System

Nanosuspensions manage the cost of a methods for regulating expanded groupings of inadequately water-solvent medications to the cerebrum with diminished foundational impacts. Critical viability has been appeared with microparticulate busulfan in mice regulated intrathecally. The work has progressed to Phase I in patients distressed with neoplastic meningitis, controlled by means of an Ommaya repository for intraventricular conveyance and through lumbar puncture. The tranquilize was all around endured and brought about deferred movement of illness. Epidural infusion of a 10% butamben suspension for disease torment was very much endured in mutts and people. Future work will presumably likewise include less obtrusive courses, using either uninvolved focusing on (by means of PEGylation, as has been accomplished for liposomes) or dynamic focusing to the mind following intravenous organization of nanosuspensions. In these last distributions, it was discovered that utilization of the operator Polysorbate 80 in the definition prompted affidavit of apolipoprotein E on the nanoparticles, which encouraged mind take-up by receptors on the cerebrum endothelial cells.<sup>[9]</sup>

### Marketed Preparations<sup>[4]</sup>

| Product  | Drug              | Indication                        | Company                      |
|----------|-------------------|-----------------------------------|------------------------------|
| Triglide | Fenofibrate       | Treatment of hypercholesterolemia | First horizon pharmaceutical |
| Tricor   | Fenofibrate       | Treatment of hypercholesterolemia | Abbott                       |
| Megace   | Megestrol Aceyate | Appetite stimulant                | PARPharmaceutical            |
| Rapamune | Sirolimus         | Immunosuppresant                  | Wyeth                        |
| Emend    | Sirolimus         | Antiemetic                        | Merck                        |

### Overview of technologies and selected examples of patents/patent applicatons on which various homogenisation processes are based.<sup>[59]</sup>

| Nanocrystal               | Company                 | Patent/Patent application examples |
|---------------------------|-------------------------|------------------------------------|
| Hydrosol                  | Novartis (Prev. Sandoz) | GB 22 69 536<br>GB 22 00 048       |
| Nanomorph <sup>TM</sup>   | Soligs/Abbott           | D 19637517                         |
| Nanocrystal <sup>TM</sup> | Elan Nanosystems        | US 5,145,684                       |
| Dissocubes                | SkyePharma              | US 5,858,410                       |
| Nanopure                  | Pharmasol               | PCT/EP00/0635                      |
| NANOEDGE <sup>TM</sup>    | Baxter                  | US 6,884,436                       |

### Future Direction

Nanosuspensions is by all accounts novel and yet monetarily suitable way to deal with battling issues, for example, poor bioavailability that are related with the conveyance of hydrophobic medications, including those that are inadequately solvent in fluid just as natural media. The disintegration issues of ineffectively water solvent medications have been generally understood to improve tranquilize ingestion and bioavailability. Nanosuspension innovation can be joined with conventional measurement frames: tablets, containers, pellets, and can be utilized for parenteral items. To exploit nanosuspension sedate conveyance, basic

definition innovations and assortment applications, nanosuspensions will keep on being enthusiasm as oral plans and non-oral organization create later on.

### CONCLUSION

Nanosuspensions of unadulterated medication offer a technique to figure ineffectively dissolvable medication and upgrade the bioavailability of a few medications. It has numerous details and restorative points of interest, for example, basic strategy for planning, less prerequisite of excipients, expanded disintegration speed and immersion solvency, improved attachment, builds bioavailability prompting an abatement in the portion

and quick nourished inconstancy and simplicity of huge scale producing. This innovation is picking up criticalness as the quantity of atoms with solvency and bioavailability related issues are expanding step by step. In this manner nanotechnology can assume an imperative job in medication disclosure projects to increment fluid solvency just as bioavailability of inadequately solvent medications.

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