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NANOSUSPENSION: AN AUSPECIOUS PRESENT - DAY STRATEGY TO IMPROVE SOLUBILITY AND TO ENHANCE BIOAVAILABILITY OF POORLY SOLUBLE DRUG ALONG WITH SAFETY AND EFFICACY: A REVIEW

Vishakha Devi*, Gopal Thakur[*]
Amar Saheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar) Punjab, 140111

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Abstract:
The present article describes that how the nanosuspension technique is the most useful technique to deliver the drug having poor solubility. As we all know, that according to the BCS classification two and four most of the drug have poor solubility. Due to the poor solubility, these drugs are not absorbed well and have low bioavailability. To resolve this complication, many techniques are used such as micronization, use of penetration enhancers, use of solvent and co solvents etc. but those plans of action are most effectively beneficial for magnify the solubility of hydrophobic drugs. So, nanosuspension is the most effective method left which supply the medicine with better solubility and bioavailability. Utmost typically to prepare best nanosuspension formulations either media milling technique is used or if it is not employed then in place of this high-pressure homogenization technique gives the best result. In nanosuspension the drug are put up in dispersion and stabilizes via way of means of surfactants. This article, signifies how the nanosuspensions will prepared or what are the techniques employed to prepare best nanosuspensions formulation, secondaly it explains that if we prepared nanosuspensions then how we know that the nanosuspensions are actually prepared i.e characterization and at last this article explain how these nanosuspensions are deliver into our body i.e applications. Nanosuspension intensify now no longer simply the solubility however additionally the safety and efficacy of the drug. The nanosuspensions are deliver via oral route, transdermal route, parenteral route, pulmonary route, ocular route etc.

Keywords: *Nanosuspension technique, Solubility, Homogenization, BCS, Bioavailability.*

Corresponding author:
Vishakha Devi,
Amar Saheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar) Punjab, 140111

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INTRODUCTION:

BCS two and four tell us about the hydrophobic drugs (water hating drugs). Due to the poor solubility of these drugs, they cannot easily achieve dissolution and therefore they cannot easily pass-through dissolving media and cannot easily absorb. To resolve this complication, many techniques are used such as micronization, use of penetration enhancers, use of solvent and co solvents etc. but those plans of action are most effectively beneficial for intensify the solubility of hydrophobic drugs. Moreover, some other techniques are adopted like vesicular system such as liposomes, dispersion of solids, emulsion, micro-emulsion. These techniques unveil favorable effects but vital issue of these approaches is that these are insufficiently universal in their applicability to all drugs[1].

Nanosuspension technology is employed to resolve these drawbacks. It include poorly soluble drugs which are suspended in dispersion and stabilizes by surfactants [2] such as sodium cholate (SC), sodium lauryl sulphate (SLS) as well as polymers like polyethylene glycol 4000 (PEG), polysorbate 80, polyethylene glycol 1000.

Definition-

Nanosuspensions are exceptionally fine colloid, biphasic solid drug fleck which can be strew in an watery (aqueous)media[2]. These nanosuspensions are made by two processes" top - down process" and " bottom - up process " having size below 1000nm and having standard size between 200-600nm[3].

Nanosuspension is the one and only choice to deliver a drug when it has many drawbacks such as large molecular weight, high dose, high logP, high melting point. Many drug transport complications assoiated with API are resolve with the aid of using nanosuspension plan of action with the aid of using preserving it in a crystalline state.

Advantages of nanosuspensions [4]:

- It is beneficial for hydrophobic drugs (water hating drugs).
- It clears up the bad solubility problems.
- Stabilizers are used in nanosuspensions which is responsible for the surface charge on particles as a result intensify the physical stability of the drug.
- Nanosuspension provide better bioavailability when it administer orally.
- In the case of ocular and inhaled delivery, it provides more constant dose.
- Nanosuspensions administer the drug through any route.

Disadvantages of nanosuspensions:

- In the nanosuspension formulation, there are some complications arises such as Physical stability, sedimentation, agglomeration and compaction.
- An adequate care must be infatuated during handling and transport due to its bulkiness.
- Exact and consistent dose won't be acquire until suspension.

Techniques for preparation of nanosuspension:

Two techniques are employed:

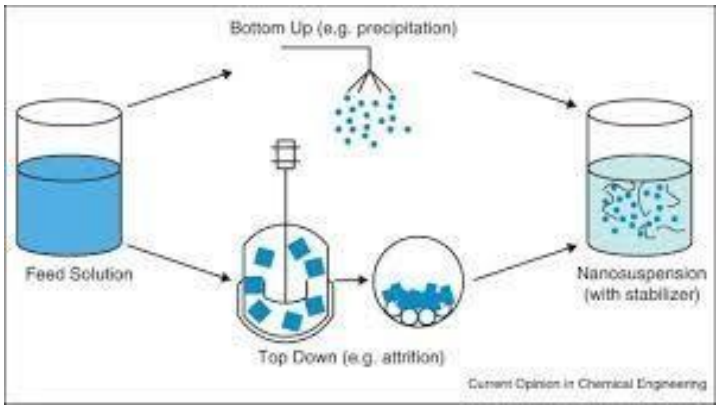
1. Top- down process technology.
2. Bottom- up process technology.

Top- down simply means conversion of something form higher state to lower state, so the "top- down process" for preparation of nanosuspensions explain that the large particles and microparticles (which are in the higher position) are shift into nanosized particles (lower position) by disintegration [5]. This process involve:

- High pressure homogenization.
- Nano edge.
- Nano pure.
- Media milling (Nanocrystals)

Similarly, the bottom- up means conversion of something from lower state to higher state, so the "Bottom- down process" explain that the molecules (lower state) are shift into nanoparticles (higher state) [6]. This process involve:

- Emulsification solvent evaporation technique.
- Super critical fluid process.
- Lipid emulsion/ microemulsion template.



High pressure homogenization [7,8]:
It involves three steps:

Secondly, this presuspension homogenizes at low pressure for premilling in high pressure homogenization.

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At last, homogenization is performed at high pressure for 10 to 25 cycle upto the nanosuspension of favored size are formulate.

Homogenization in aqueous media (Dissoi cubes):
R.H. Muller in 1999 prepare nanosuspensions by appoint a piston –gap kind homogenizer [9]. For the manufacturing of nanosuspension, he first makes combination of drug and surfactant and this combination is compelled via a small inlet orifice of high-pressure homogenizer at very excessive pressure.

Principle:
The drug particle are shatter through three methods for the duration of homogenization –

- By Cavitation
- By high shear forces
- By collision of the particle towards every other.

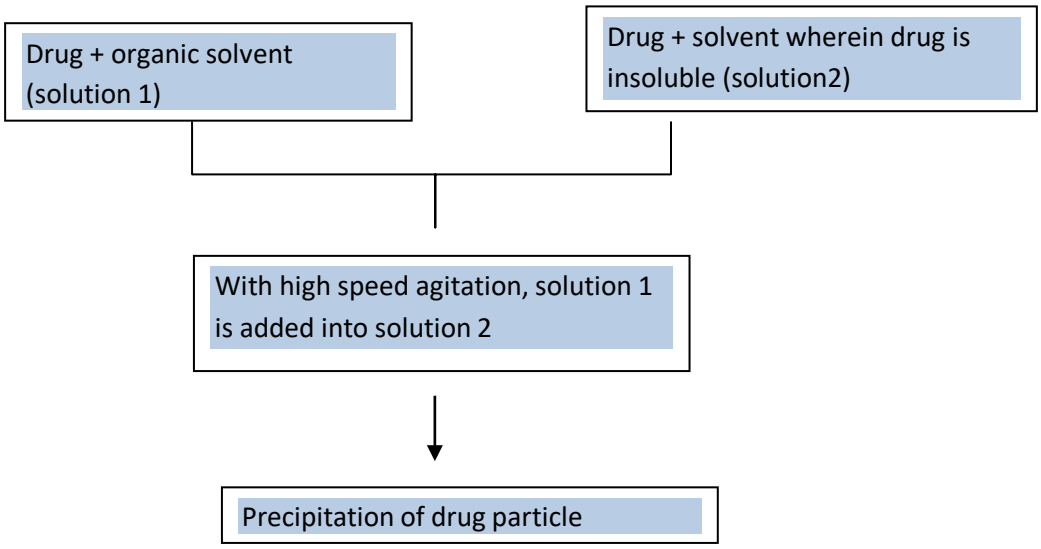
The mixture of drug and surfactant is carried in a cylinder of 3mm, which instantly passes at high pressure through a gap of 25 µm which steer to high streaming velocity. In this gap, the pressure applies by fluid when it is in motion (dynamic pressure) is increases and static pressure (pressure apply by fluid when it is in rest) is decreases beneath the boiling factor of the H_2O at room temperature simultaneously. Because of that, the water begins boiling at room temperature and shape gas effervescence. These gas bubbles collapse and the forces produce due to the implosion shatter the microparticle into nanoparticles, this is called cavitation. The forces (shear forces) which can be produced due to the collapse of the particle at excessive velocity facilitate to achieve the nanosizing of drug[10].

Homogenization in non- aqueous media (nanopure):
As the name suggest, this is a technique in which the mixture of drug and surfactant is homogenized in non- aqueous media or as we can say water free media. In this strategy, the mixture (drug + surfactant) is homogenizing in polymers instead of water like polyethylene glycol 400 (PEG 400), polyethylene glycol 1000(PEG 1000) etc. This homogenization is named as "deep- freeze" homogenization (deep freeze means to freeze something at 0°C or below), so in this the mixture (drug +surfactant) is homogenize at 0°C room temperature and below the freezing point i.e. -20°C[11].

Micro - precipitation – high pressure homogenization (Nano edge) [12,13,14]:

In this, two strategies are integrated:

- Microprecipitation.
- High pressure homogenization techniques [15].



Milling technique:

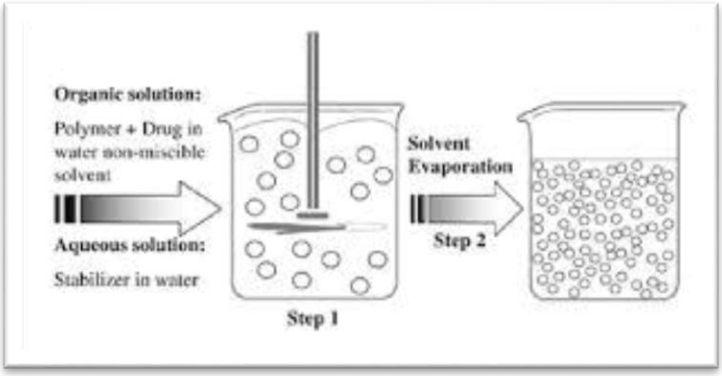
a. Media milling:[16,17]
In media milling plan of work, the drug debris are bump along with the media milling. Because of the collapse between particles, high energy and the shear forces are generated. The forces produce the nanosizedparticles from microparticles via delivering plenty of energy.

Drug, stabilizer, water or suitable buffer are added to the cell of milling and this mixture is circled at excessive shear rate to make suspension.

b. Dry co - grinding:[18-20]
As the name suggest that these are dry co – grinding techniques, which means that these techniques are performed in the absence of organic solvents. For long time, nanosuspensions are prepare with the help organic solvents and this process is known as wet grinding but nowadays, nanosuspensions are produced by dry co-grinding method which use numerous polymers and co-polymers instead of organic solvent[13]. This process intensifies ground polarity and remodeling of fundamental a part of crystalline kingdom of drug to amorphous form.

Emulsion - solvent evaporation technique [21]:
In the initial step, the organic solvent and co solvent are employed to disseminate the drug. This solution of drug is emulsified or disperse in some other liquid that's non solvent for drug. Quick evanescence of solvent bring about the precipitation of drug or to offer nanosuspension.

High shear forces are produced with the aid of using the usage of a excessive pace stirrer to manipulate crystal boom and particle aggregation.



Lipid emulsion/ microemulsion template[21]:
Micro emulsion are the dispersion of the two unmixable liquids like water and oil which may be stabilized with the aid of using surfactant and co-surfactant. The drug is stuffed into every preformed or inner segment of the microemulsion and can be saturated via way of plan of work intimate blending of drug.

Super - critical fluid process:[22]
When the vital temperature and pressure of fluid is less then its normal temperature and pressure then this process in known as super critical fluid process. The super critical fluid are non-condensable smeared fluid whose temperature and pressure are supplementary then its vital temperature and vital pressure. The depletion in particle size become carried out through solubilization and nanosizing methods via super critical fluid process.

Characterization of nanosuspensions:

1. **Mean particle size and particle size distribution: [23-26]**

After the formulation of nanosuspension, the first important thing which is to be characterize is the size of nanosuspension particle which tell us that the nanosuspension formulated is within the size range limit i.e. Less than 1000nm. The particle size and diameter of the particles (poly-dispersity index) are examine via:

- Laser diffraction (LD)
- Photon correlation spectroscopy
- Microscope
- coulter counter

If the PI value of the nanosuspension is low then it shows that the nanosuspensions are stable for long period of time.

The microparticles of drugs are discover and quantify through laser diffraction for the duration of process. It can be employed to deliberate the particles of 0.05 to 2000 µm.

PI Value	Size distribution
0.1 up to 0.25	Narrow distribution
More than 0.5	Very broad size distribution

stain of nanosuspension. It provide the outright number of particle by virtue of extent for The coulter counter method is more appropriate than Laser diffraction to quantify the different size classes.

2. **Crystalline state and particle morphology:[26-28]**

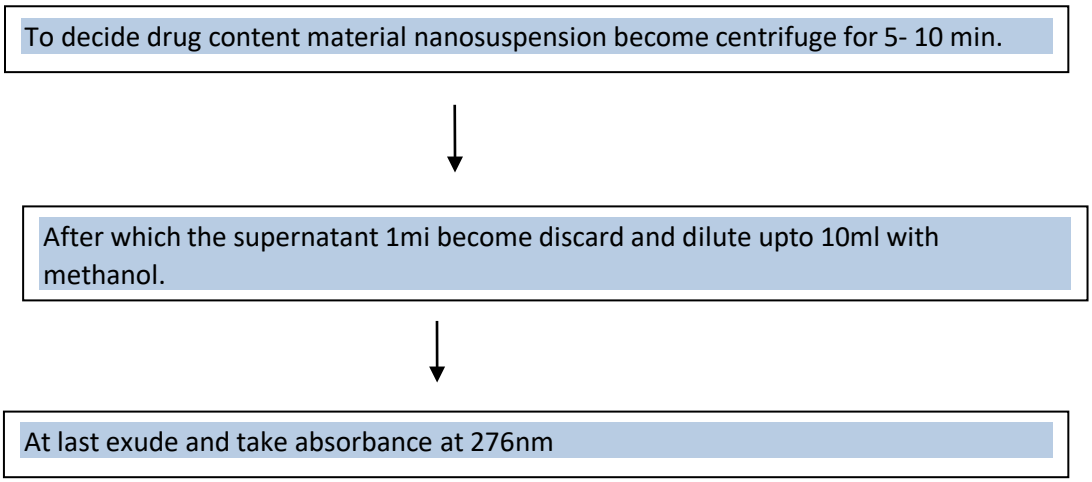
The crystalline state and particle morphology are hired to take a look at the form and structure of the nanoparticles. This characterization parameter tell us that the particle in nano size range present in which form and what is the structure of these particles. During high pressure homogenization the crystalline shape of nano particle may transmute both into polymorphic or amorphous form. The volume of the amorphous element and the fluctuation in the solid state of particle is decided with the aid of using X ray diffraction analysis.

3. **Surface charge (Zeta potential):[29-32]**

By using Zeta potential characterization parameter we come to know about the surface charge. The Zeta sizer tell us about the size of the nanosized particles The charge on the surface of the particle is due to the surfactants added in the formulation. The charge on the surface of the particle helps to prevent clumping of the particle in the formulation which make the formulation more stable for long period of time. The nanosuspensions which are stabilizes Electrostatically required $\pm$ 30 mv minimal zeta potential, and $\pm$ 20 mv zeta potential minimal for nanosized particles which are stabilizes sterically. In this characterization parameter, firstly the electrophoretic mobility will figure out, then later this electrophoretic mobility

is metamorphosed into zeta potential.

4. **Drug content[33]:**



Pharmaceutical application of nanosuspensions:
Once nanosuspensions are formed, those nanosuspensions are included or organized into diverse dosage forms such as oral dosage form, parenteral, intravenous, ophthalmic, pulmonary, topical, intrathecal dosage forms by the usage of postproduction processes. The nanosuspensions are in nano size range and have large surface area that being the case they enhance dissolution rate and absorption of drugs.[34]

Oral drug delivery: [35-39]
This administration signifies that the drug are taken via oral route (mouth). When the drugs having poor solubility are taken through oral route then many vital trouble are arises such as poor dissolution rate, minimum absorption of drug and less efficacy etc. As we all know, that in oral drug delivery there is no pain involve, so it is the first patient choice drug. The nanosuspensions are in nano size range and have large surface area, thus the oral nanosuspensions are applied to improve absorption along with bioavailability of hydrophobic drugs. When the azithromycin nanosuspensions are compared with the micronized drugs then we found that 65 ^{0}/0 or above than this the drug was dissolve.

Example: Carbamazepine, Megestrol acetate, Insulin, Keto-profane, Azithromycin

Pulmonary drug delivery: [40-45]
Pulmonary drug delivery simply signifies that the drug is reach to the systemic circulation of our body via alveolar epithelium (a layer which cover almost all the surface area of the lungs and act as a protecting layer) of the lungs. For the pulmonary delivery of nanosuspensions, these are nebulized by nebulizer (nebulizer is a machine which convert the liquid medicine into mist). So the person having some lung disease, asthma or COPD, he only need to sit with the machine and breathe in by a connected mouthpiece. As we all know, that in this route the drug is deliver through lungs, so to deliver the drug through this route most commonly aerosols are employed.

Example: Budesonide, Fluticasone

Parenteral delivery: [46-48]
Parenteral delivery of drugs the delivery system in which the drug is deliver through various route such asintravenous (IV), subcutaneous (SC), intramuscular (IM) etc. these delivery include injection as well as implantation through skin or other external body tissue. The parenteral nanosuspensions are employed to resolve many complication associated with the normal parenteral delivery such as solubilization volume, parenteral admissibility, lofty manufacturing cost etc. Along with these the parenteral nanosuspension enhance the potency of the parenterally administered drugs.

Example: Naproxen, Clofazimine, Loviride, Oridonin, Omeprazole

Ocular drug delivery: [49-51]

Ocular delivery signifies that the drug is reach to the systemic circulation via ocular route(eye). The main motive to deliver the nanosuspensions via ocular path is the sustained discharge of the drug. The major disadvantage of the ocular delivery is that the drug is come out with the tear fluid which is secreted by lachrymal gland, as a result the drug stay for less time in the eye and unable to dissolve properly which result in the low bioavailability of the drug. So the nanosuspension kept the drug in the eye for long period of time, as a result of this less drug ruin and more absorb and at last bioavailability increases.

e.g. Liang and his co - workers used Eudragit polymer to prepare nanosuspensions of cloricromen. They insert the nanosuspension of cloricromen in the rabbit eye and examine that the drug have lofty availability in the aqueous humor of rabbit eye.

Example: Hydrocortisone, Prednisolones

Targeted delivery: [52,53]

Targeted delivery is those in which drug is deliver to the specific target site either it is tissue, cell or organ. Keyser prepare the nanosuspensions of aphidicolin for the leishmania infection which enhance the drug targeting to the macrophage.

Scholler et al. use nanosuspension of atovaquone to treat toxoplasmic encephalitis to explain the drug targeting to brain.

Transdermal delivery:

Transdermal delivery signifies that the drug is reach to systemic circulation of our body via transdermal route (through intact with skin). In this, patches are formulated for the delivery of drug and the nanosuspensions are suspended in these patches. Diclofenac sodium an anti-inflammatory drug and atorvastatin drugs are deliver through this process [54].

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