CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.888219

Available online at: http://www.iajps.com Review Article

NANO-DISPERSIONS (SUSPENSIONS): AN EMERGING TRENDIN ENHANCING DRUG SOLUBILITY AND DRUG TARGETING

Kousar Begum*[1], Sathyabratha Jena[2], Konatham Monika [2],B.Jagadeesh Babu[1],M.Reshma[1] and A.Aravanthi[1]

[1] Faculty of Pharmacy, RGR Siddhanthi College of Pharmacy, Secunderabad, Telangana, India.
[2] Nalanda College of Pharmacy, Nalgonda, Telangana, India

Abstract:
Nano technology is an innovation for the drug targeting to release the drug in short duration of time at a specific site. Nano sized particles are having the more dissolution velocity to increase the drug action and these are majorly useful for the poorly solubilised drugs to increase its solubility and enhance the bio availability. This article explains about the nanosuspensions, in which drug particles are distributed uniformly throughout the vehicle. Which exhibit its maximum solubility and ready to use through any route of administration? Recently nanosuspensions are ment for oral route for administration. This review explains about the stability of nano suspensions compared to other oral liquid dosage forms, classification, methods of preparation with its major advantages, limitations, properties of nanosuspensions, evaluation methods and its pharmaceutical applications.

Key words: *Nano technology, nano suspension, classification, methods of preparation, evaluation parameters*

Corresponding author:
Kousar Begum,
Faculty of Pharmacy,
RGR Siddhanthi College of Pharmacy,
Secunderabad, Telangana, India.
E-Mail: kousar.ceutics@gmail.com

QR code

Please cite this article in press as Kousar Begum et al, ***Nano-Dispersions (Suspensions): An Emerging Trendin Enhancing Drug Solubility and Drug Targeting****, Indo Am. J. P. Sci, 2017; 4(09).*

INTRODUCTION:

Nanotechnology is likely to revolutionize our lives and It is emerging discipline that encompasses an increasingly sophisticated ability to manipulate matter at the nanoscale (0.1 nm to 1000 nm) resulting in new material, product. It is one of the most important research and development area in modern science. This implies the medical application of nanotechnology and related research leading to the designing, testing and optimizing of the pharmaceutical formulations. [1]

Nano sized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. [2]

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,

1 micron = 1000 nm.

Micron = 10-6m= 10-4 cm = 10-3mm.

1 nm = 10-9m= 10-7 cm = 10-6 mm.

0.1 nm = Diameter of one Hydrogen atom.

For a long duration of time micronization of poorly soluble drugs by colloid mills or jet mills was preferred. The overall particle size distribution ranges from 0.1 µm to approximately 25 µm, only negligible amount being below 1 µm in the nanometer range[3].

A pharmaceutical nanosuspension is defined as a coarse biphasic dispersion of finely dispersed insoluble drug particles as the internal phase, suspending in an aqueous vehicle for either oral or topical or parentral or pulmonary administration [4].

Particle size of nanosuspension below 1µm stabilized by the use of surfactants but average particle size ranging from 200 to 600nm where the solubility is an essential factor for drug effectiveness, independent of the route of administration. In nanosuspension the drug is maintained in the required crystalline state with reduced particle size which increases the surface area by which increase the dissolution rate hence improved in bio-availability. Poorly soluble drugs are often challenging task for formulations in the industry [5 [,[28].

Nanosuspension technology can be used to enhance the solubility of the poorly soluble drugs in aqueous as well as lipid media and also to improve the stability as well as the bioavailability of poorly soluble drugs. As a result the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g: oral/i.v) administration. Nano size particles can increase dissolution velocity and saturation solubility because of the vapor pressure effect. [6]

UTILITY OF SUSPENSIONS

A suspension is often chosen as pharmaceutical dosage form for drugs insoluble in water and aqueous fluids at the dosage required for administration and when attempts to solubilize the drug would compromise stability and safety. The large surface areas of the dispersed drug particles often facilitate absorption. Unlike drug particles contained in tablets or capsules, the dissolution of drug particles in suspension and subsequent absorption commence upon dilution in gastrointestinal fluids. Finely divided particles dissolve faster and have higher relative solubility than do similar macro particles. The parenteral suspension is an ideal dosage form for prolonged or ''depot'' release. In the administration of a drug as an aqueous or oleaginous. Suspension into subcutaneous or muscular tissue, the drug is deposited at the injection site. The depot acts as a reservoir, slowly releasing drug at a rate related to both the intrinsic aqueous. [7]

HOW NANOSUSPENSIONS ARE STABLE THAN OTHERS????

The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Ostwald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles.

The review focuses on advantages, method of preparation, physical characteristics and evaluation of nanosuspensions [8], [28].

Major Advantages of Nanosuspensions

1. Can be applied for the poorly water soluble drugs.
2. Can be given by any route by Dose reduction
3. Reduced tissue irritation.
4. Rapid dissolution and tissue targeting.
5. Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
6. The absorption from absorption window of the drugs can be increased, due to reduction in the particle size.
7. Improvement in biological performance due to high dissolution rate and saturation solubility of the drug. 8
8. Long term physical stability due to absence of Ostwald ripening.

9. Nanosuspensions can be incorporated in tablets, pellets, hydrogel and suppositories are suitable for various routes of administration.
10. Increasing the amorphous fraction change in the crystalline structure and higher solubility.
11. Improves chemical stability of certain drug.
12. Drug in suspension exhibits higher rate of bioavailability than Other dosage forms bioavailability is in following order, Solution > Suspension > Capsule > Compressed Tablet5
13. Duration and onset of action can be controlled.
14. Mask the unpleasant/ bitter taste of drug.
15. Enhance the solubility and bioavailability of drugs
16. Suitable for hydrophilic drugs
17. Provides a passive drug targeting [7]

Need of Nanosuspension

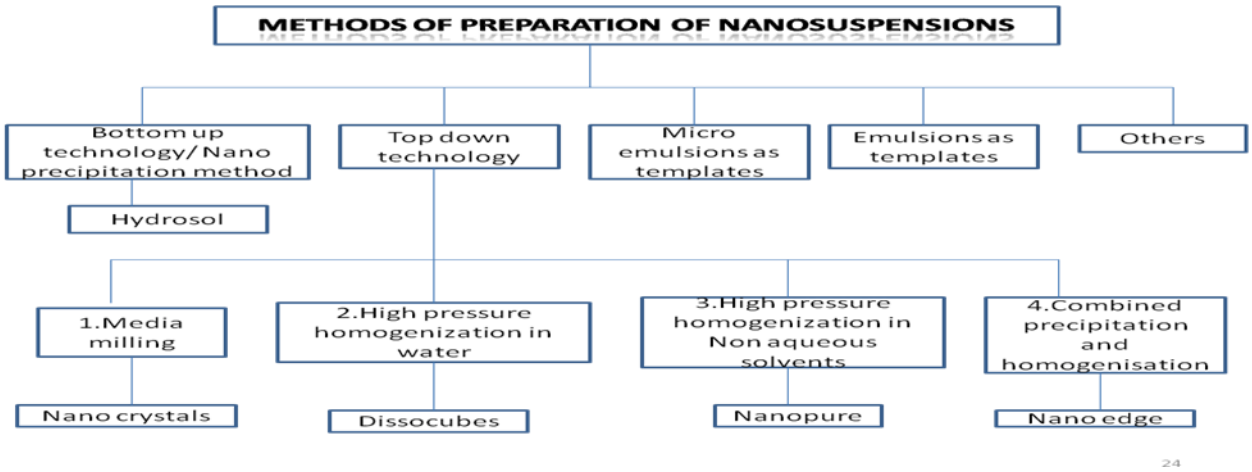
More than 40% of drugs are poorly soluble in water, so they show problems in formulating them in conventional dosage forms. Also, for class II drugs which are poorly soluble in aqueous and organic media, the problem is more complex. Preparing nanosuspension is preferred for such compounds that are insoluble in water (but are soluble in oil) with high log P value. Various approaches to resolve problems of low solubility and low bioavailability micronization, co-solvency, oily solution, salt formation- some other techniques are liposomes, emulsions, microemulsion, solid dispersion, ß-cyclodextrin inclusion complex etc. But, many of these techniques are not universally applicable to all drugs. In these cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in inorganic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or intravenous (IV) administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators. [6], [9]

Major issues with poorly water-soluble compounds:

1. Poor bioavailability.
2. Inability to optimize lead compound selection based on efficacy and safety
3. Fed/fasted variation in bioavailability
4. Lack of dose-response proportionality
5. Suboptimal dosing
6. excessive use of co-solvents and other excipients
7. Use of extreme basic or acidic conditions

Therefore, for the production of nanosuspension, the type and concentration of the stabilizer is a critical stage for the successful production of nanosuspension. Both polymeric and surfactant stabilizers can be used for this purpose. [10], [11]

Route of Administration	Disadvantages of Conventional Formulations	Benefits of Nanosuspensions
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improved solubility and Reduced fed/fasted ratio
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ dose consistency and Lesser irritation
Intravenous	Poor dissolution/ non-specific action	Rapid dissolution/ tissue targeting so Prolonged retention time
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation High bioavailability Rapid onset of action
Inhalations	Low bioavailability due to low solubility	Rapid dissolution/ high bioavailability/ dose regulation [13]



CLASSIFICATION OF SUSPENSIONS

I. Based On General Classes

- Oral suspension
- Externally applied suspension
- Parenteral suspension

II. Based On Proportion Of Solid Particles

- Dilute suspension (2 to10%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) [14], [15]

PREPARATION OF NANOSUSPENSIONS

Sucker and co-workers used a precipitation technique to produce nanoparticles by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle. This has the advantage of using relatively simple and low-cost equipment. The major challenge of this technique is to avoid crystal growth that occurs on storage due to Ostwald ripening. [17], [18]

1. Bottom Up Technology/ Nanoprecipitation method

The conventional methods of precipitation (Hydrosols) are under Bottom Up technology. Using a precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent. In the water-solvent mixture the solubility is low and the drug precipitates. Precipitation has also been coupled with high shear processing. [19]

1.1 Hydrosol method

This is **similar to the emulsification- solvent evaporation method.** The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size. [18], [20]

The nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix. Apart from this, it has all other advantages of a liquid dosage form over the solid dosage forms. The present review is focused on various methods of preparing nanosuspensions, critical parameters to be characterized and the application of nanosuspension formulations. Most of the drugs are not soluble in water and they create major problem during formulation they also show poor bioavailability. Reduction in particle size of such drugs enhances the dissolution rate and bioavailability. Nano suspension a promising delivery used to enhance the solubility of hydrophobic drugs. [6], [16]

2. Top Down Technology [16], [18], [21],[22],[23]

2.1. Media milling/ Wet milling

High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The major concern with this method is the residues of milling media remaining in the finished product.

2.1.1. Nanocrystal is a patent protected technology developed by Liversidge et al. (1992).

In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a processing. Rapid addition of a drug solution to a solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids.

The mill can be operated in a batch or recirculation mode. Crude slurry consisting of drug, water and stabilizer is fed into the milling chamber and processed into nano-crystalline dispersion and the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of <200nm is 30–60 min.

Principle
The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked polystyrene resin. Once the formulation and the process are optimized, very little batch-to-batch variation is observed in the quality of the dispersion.

Major Advantage
Narrow size distribution of the final nano-sized product.
Limitation

- Degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5 μm.

2.2 High pressure homogenization: High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer.

2.2.1. Dissocubes technology is an example of this technology developed by R.H. Müller in 1999 using a piston-gap-type like APV Gaulin types has been used. high pressure homogenizer, which was recently released as a patent owned by SkyePharm.

Principle
This method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required.

Major Advantage
It does not cause the erosion of processed materials.

- Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.

Limitation

- Pre-processing like micronization of drug is required.

2.3 Homogenization in non-aqueous media
2.3.1 Nanopure:

Principle:
In this, suspensions are homogenized in water free media or water mixtures i.e. the drug suspensions in the non- aqueous media were homogenized at 0º C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to DissoCubes and hence can be used effectively for thermolabile substances at milder conditions.

Major Advantage
The dispersion medium need not be removed.

- Evaporation is faster and under milder conditions (when water and water miscible liquids are used).

2.4 Combined precipitation and homogenization
The drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture, the solubility is low and the drug precipitates. Precipitation has also been coupled with high shear processing. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol. This is accomplished by a combination of rapid precipitation and high-pressure homogenization.

Nanoedge:
The Nanoedge patented technology by Baxter depends on the precipitation of friable materials for fragmentation under conditions of high shear and/or thermal energy.
Principle:
This is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid addition of a drug solution to an anti-solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high super saturation when the solubility of the amorphous state is exceeded. The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time.

Major Advantage

- They are in completely amorphous,.

Limitation:
The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology.

Type of solvent	Name	Remarks
Water-miscible solvents	Ethanol, Iso-propanol	Pharmaceutically acceptable, less hazardous
Partially water-miscible solvents	ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate.	Preferred less hazardous such as dichloromethane.

3. Microemulsion as template/Lipid emulsion

Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants. Nanosuspensions are obtained by just diluting the emulsion. Suitable dilution of the micro emulsion yields the drug nanosuspension. An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate.

Major Advantage

Needed less energy input for the production of nanosuspensions by virtue of microemulsions.

Limitation

Large amounts of surfactant or stabilizers are required.

4. Emulsion as template

Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion.

There are two ways of fabricating drug nanosuspensions by the emulsification method. In **the first method**, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride and chloroform were used.

Second method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents. The emulsion is formed by the conventional method and the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension.

Major Advantage

- Particle size can easily be controlled by controlling the size of the emulsion droplet.

Limitation

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.

5. Others:

5.1. Nanojet Technology

This technique, called 'opposite stream or Nanojet technology', uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure up to 4000 bar at the high velocity of 1000m/s. The high shear force produced during the process results in particle size reduction. Equipment using this principle includes the M110L and M110S microfluidizers (Micro fluidics).

E.g: Dearn prepared nanosuspensions of atovaquone using the microfluidization process.

Limitation:

The major limitation of this technique is the high number of passes through the microfluidizer (upto 75 passes) and that the product obtained contains a relatively larger fraction of microparticles. And also takes large production time. [6], [16]

5.2. Emulsification-solvent evaporation technique

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer. [6]

5.3. Supercritical fluid method

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense non condensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). A SCF process allows micronization of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter.

Limitation

- Use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques. [16]

5.4. Dry co-grinding

Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported.

Itoh et al. reported the colloidal particles formation of many poorly water soluble drugs like Glibenclamide and Nifedipine obtained by grinding with PVP and SDS.

Many soluble polymers and co-polymers such as PVP, PEG, HPMC and cyclodextrin derivatives have been used.[9],[18

Method	Advantages	Limitations	Drug[24]
High-pressure Homogenization	widely applying regions, ease of scale-up and little batch to batch variation.	pretreatment of micronized drug particles is needed.	Albendazole ,Amphotericin B, Aphidicolin ,Atovaquone
Milling	the same as those for high-pressure	potential erosion.	Cilostazol
homogenization	material from the milling pearls		Danazol ,Naproxen
Micro-precipitation	low need of energy, stable products and simple process	potential toxicity of non-aqueous solvents	Carbamazepine ,Cyclosporine Retinoic acid
Emulsion and Microemulsion	low need of energy, simple process and stable products.	high concentration undesired surfactants and residual solvents	Breviscapine ,Ibuprofen Mitotane
Micro-precipitation-highpressure homogenization	Required less mechanical force and energy compared	The manufacturing process is complicated	___
Dry Co-grinding	Easy process ,No organic solvent Require short grinding time	Generation of residue of milling media	Clarithromycin,Glibenclamide Glisentide,Nifedipine,Phenytoin

B.Organic solvents
Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. Partially water-miscible organic solvents like glycols can be used.
The pharmaceutically acceptable and less hazardous water miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl format, butyl lactate, triacetin, propylene carbonate and benzyl alcohol will be used.

C.Surfactants
Surfactants are incorporated to improve the dispersion by reducing the interfacial tension. They also act as wetting or deflocculating agents e.g. Tweens and Spans - widely used surfactants.

D.Co-surfactants
The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated e.g. Transcutol, glycofurol, ethanol and iso-propanol - safely used as co-surfactants. Also, bile salts and Dipotassium glycerrhizinate can be used as co-surfactants.

E.Other additives
Formulation considerations Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

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.

PROPERTIES OF NANOSUSPENSIONS
1. Physical Long-term Stability: Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentrated area around small particles (higher saturation solubility) to areas around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. Ostwald ripening is totally absent in nanosuspension which is also responsible for long-term physical stability of nanosuspensions.

2. Increase in Saturation Solubility and Dissolution Velocity of drug: Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation dissolution velocity increase due to increase in the surface area from micron size to particles of nanometer size.
$Dx/dt = [(D \times A)/ h] [Cs-X/V]$
Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

3. Internal Structure of Nanosuspensions: The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenisation cycles chemical nature of drug and power density applied by homogeniser.

4. Adhesiveness
There is a distinct increase in adhesiveness of ultra-fine powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for improved oral delivery of poorly soluble drugs.
A drastically remarkable report is that of the increase in bioavailability for danazol from 5 % (as macrosuspension) to 82% (as nanosuspension).

5. Crystalline state and morphology
A potential change in the crystalline structure of nanosuspensions saying increasing the amorphous fraction in the particle or even creating completely amorphous particles is a characteristic of consideration. The application of high pressures during the production of nanosuspensions was found to promote the amorphous state.[25]

Post-Production Procession
Post-production processing of nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the nanosuspension for a long period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophilization or spray drying may be employed to

produce a dry powder of nano-sized drug particles. [26]

1. Solidification Techniques
In this case, solid dosage forms are considered more attractive, due to their patient convenience (marketing aspects) and good stability. Therefore, transformation of nanosuspensions into the solid dosage form is desirable. Solidification methods of the nanosuspensions include some unit-operations such as pelletization, granulation, spray drying or lyophilization. As the primary objective of the nanoparticulate system is rapid dissolution, disintegration of the solid form and redispersion of the individual nanoparticles.

2. Surface Modification Techniques
Nanosuspensions have the particular characteristics to increase the saturation solubility and dissolution rate for the poorly soluble drugs. But in some cases, the rapid or burst release of nanosuspensions may result in the side effect and toxicity. As a colloid nanoparticle system, nanosuspensions usually can target the Monocyte Phagocytic system (MPS), which can aid in the treatment of lymphatic-mediated diseases, like Mycobacterium tuberculosis, Listeria monogyna, Leishmania sp. The action is called as 'passive targeting'. For example, Tan et al. had prepared layer-by-layer self-assembly coated procaine hydrochloride. [9]

EVALUATION OF NANOSUSPENSION
1. *In-vitro* evaluations [25], [26]
1.1. Mean Particle size and size distribution
1.2. Particle charge (Zeta Potential)
1.3. Crystalline state and morphology
1.4. Saturation solubility and dissolution velocity
1.5. pH
1.6. Osmolarity
1.7. Drug content
1.8. Stability studies
2. *In-vivo* evaluation [6]
3. Evaluation for surface-modifird nanosuspension [26]
3.1. Surface hydrophilicity
3.2. Adhesion properties
3.3. Interaction with body proteins

1. *In-vitro* evaluation
1.1. Mean particle size and size distribution
The mean particle size and the width of particle size distribution (called Polydidpersity Index(PI)) are determined by Photon Correlation Spectroscopy (PCS). Particle size and PI governs the saturation solubility, dissolution velocity and biological performance. A PI value of 0.1–0.25 indicates a narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD). LD measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force microscopy is used for visualization of particle shape.

1.2. Particle charge (zeta potential)
The determination of the zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspensions exhibiting good stability, for an electrostatically stabilized nanosuspensions minimum zeta potential of 30mV is required whereas in the case of a combined electrostatic and 20 mV is desirable.

1.3. Crystalline state and particle morphology
The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug. Differential Scanning Calorimetry (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The XRD is also used for determining change in physical state and extent of amorphous drug.
Techniques like SEM, AFM or transmission electron microscopy (TEM) are preferred for determining the exact size and morphology of nanoparticles in suspension.

1.4. Solubility and Dissolution velocity
Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. Determination of these parameters is useful to assess *in vivo*.
The dissolution velocity and the saturation solubility are enhanced by formulation of nanosuspensions. Reduction in particle size results the increased dissolution pressure and enhance the solubility. Change in surface tension occurs as the solubility increases (due to particle size reduction) which lead to increased saturation solubility. Different physiological solutions at different pH and different temperatures are also effects the saturation solubility and dissolution velocity.
The Ostwald-Freundlich equation is:
$C(r) = C(\infty) \exp (2\gamma M / r\rho RT)$

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.

1.5 pH: Prepared nanosuspension was taken in 10ml beaker and pH was measured using pH meter (Digital Instrument Corporation, India).

1.6 Osmolarity: Practically Osmolarity was measured using Osmometer.

1.7 Drug content: Drug content of nanosuspension formulation was carried out by taking lyophilized powder (weigh equivalent to 5mg of drug) in Methanol: THF (1:1) mixture, shaken well, Mannitol is slightly soluble in Methanol:THF (1:1) mixture so it was then centrifuged at 8000rpm for 10min. The supernatants were taken and diluted with Methanol: THF (1:1) mixture and the absorbance was measured at 210nm. The drug content was calculated using the calibration curve.

1.8 Stability Study: Stability of optimized nanosuspension formulation was evaluated by determining change in particle size during storage at 2-8°C. Any change in particle size of nanosuspension formulation was observed using Malvern Master sizer 2000 at periodic time intervals.
Nanosuspensions Stability depends on the particle size of the suspended particles. Nanosuspensions can be stored at different stress conditions like different temperature (15, 25, 35 45°C), thermal cycling, and mechanical shaking and change in their mean particle size can be followed for three months.

2. *In-vivo* evaluation [6]
The *in vivo* evaluation of the nanosuspensions is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometry.

3. Evaluation of the Surface Modified of Particles [26]

3.1 Surface Hydrophilicity: For intravenously injected nanosuspensions, additional parameters need to be determined which affect the *in vivo* fate of the drug nanoparticles. The surface hydrophobicity determines the interaction with cells prior to phagocytosis and in addition, it is a relevant parameter for the adsorption of plasma proteins the key factor for organ distribution.

3.2 Adhesion properties: *In vivo* bioadhesive study is performed where Male Wistar rats can be used. In general, each animal receives a single oral dose of 1ml aqueous suspension containing 10 mg of the nanoparticles loaded with the drug (approximately 45 mg particles/kg body Weight). The animal is sacrificed by cervical dislocation at 1 and 3 h post-administration. The abdominal cavity iscecum is removed, opened lengthwise along the mesentery and rinsed with phosphate saline buffer (pH 7.4). Further, the stomach, small intestine and cecum is cut into segments of 2 cm length and digested in suitable alkali for 24 h. Drug is extracted from the digested samples by addition of 2ml methanol, vortexed for 1 min and centrifuged. Aliquot (1 ml) of the supernatants is to be assayed for the drug by spectrofluorimetry to estimate the fraction of adhered nanoparticles to the mucosa. For calculations, standard curves of the drug can also be prepared.

3.3 Interaction with body proteins : *In vitro* interaction between nanoparticles and mucin can be studied by incubation of mucin and nanoparticles (1:4 weight ratio) either in acidic or in neutral medium. The incubation is carried out under stirring at temperature of 37ºC. The dispersions is then be centrifuged and 150µl of each supernatant is placed in a test plate. Micro BCA Protein Assay Reagent Kit (150µl) then added to the supernatants and the plate, is incubated for 2 h at 37º C. According to this procedure, the absorbance of mucin can be measured by colorimetry at λmax of the drug. The amount of the mucin adsorbed to the nanoparticles can be determined as a difference between its initial concentration and the concentration found in the dispersion after incubation and centrifugation. The calculations can be made on the basis of mucin standard curves.

PHARMACEUTICAL APPLICATIONS

1. Oral Drug Delivery [16],[18]
The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the GIT. Due to smaller particle size and much larger surface to volume ratio, oral nanosuspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs.

2. Parentral drug delivery [16], [18]
Parentral route of administration is used when rapid onset of action is required, when drug has extensive first pass metabolism or it is not absorbed by gastrointestinal tract. The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes.

3. Pulmonary Drug Delivery [6], [16], [18]
For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Nebulized form of the aqueous nanosuspensions is used for the delivery of drugs to lung by Initial quick onset of action and then controlled release of the active moiety (which is required by most pulmonary diseases).

4. Ocular drug delivery [16], [18]
Although suspensions offer advantages such as prolonged residence time in a cul-desac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity created by water-soluble drugs. Nanosuspensions can be explored for the drugs that exhibit poor solubility in lachrymal fluids.

1. Prolonged residence time of drug in the cul-de-sac.
2. Avoidance of high tonicity of water soluble drugs.
3. Sustained release of the drug can be obtained by incorporation of nanosuspension in a suitable hydrogel base or mucoadhesive base.

5. Targeted Drug Delivery [6], [16], [18]
Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in vivo* behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly.

6. Bioavailability enhancement [6]
Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. The therapeutic effect was significantly enhanced, which indicated higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min).

7. Intravenous administration [6]
The parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug.

8. Mucoadhesion of the nanoparticles [6],[16],[18]
Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.

9. Topical formulations [23]
Creams and water-free ointments can be formulated by the incorporation of the drug nanoparticles into the formulations. In the topical dosage form, saturation solubility can be enhanced by the use of nano-crystalline form of the drug. It enhances the diffusion of the drug into the skin.

10. Drug targeting [18], [27]
Nanoparticulate systems have shown great potential in targeting of the drugs, especially to the brain targeting. As the surface properties and *in-vivo* behavior of nanosuspensions can be altered easily by changing either the stabilizer.

MarketedProducts
Current Marketed Pharmaceutical Products Utilizing Nano-crystalline Formulation [16]

Product	Drug compound	Indication	Company	Nanoparticle technology
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Élan Drug Delivery , Nanocrystals®
EMEND®	Aprepitant	Anti-emetic	Merck	Élan Drug Delivery , Nanocrystals®
TRIGLIDE™	Fenofibrate	Hypo-cholesteremic	FirstHorizon Pharmaceutical	SkyePharmaIDD®-P technology

Case Studies

Case 1

Polymeric nanosuspensions were prepared from Eudragit RS100 and RL100 polymer resins and loaded with Flurbiprofen (FLU), with the aim at improving the availability of the drug at an intra-ocular level for the prevention of the miosis induced during extracapsular cataract surgery.

Case 2

Cremophor® EL, Paclitaxel was formulated as a nanosuspension by high-pressure homogenization. The nanosuspension was lyophilized to obtain the dry Paclitaxel nanoparticles (average size, 214.4 ± 15.03 nm), which enhanced both the physical and chemical stability of Paclitaxel nanoparticles. Paclitaxel injection showed reduced area under the concentration, greater clearance, and shorter elimination half-life compared with the Paclitaxel solution.

CONCLUSION:

Nano suspensions are the submicron colloidal dispersions with the nano sized insoluble drug particles to enhance the dissolution solubility, saturation solubility, improve bio-availability of hydro phobic drugs, versatility in surface modification and also alters the pharmaco- kinetics of drugs thus improves the drug safety and efficacy. These are the novel dosage forms for targeting the longer variety of diseases.Recently these are attained as nanosuspension drug delivery, simple formation technologies and variety of applications. Nano suspensions will continue to be of interest as oral formulations and non-oral administrations developed in the future.The applications for the parentral and oral route have been successfully employed but pulmonary and ocular have been realized. Whereas buccal, nasal, topical deliveries are still awaiting for exploration.

REFERENCES:

1. Neelesh kumar mehra et al., carbon nanotube new contour to drug delivery, the pharma review jan-feb 2011.
2. shivanand pandey et., al nanosuspension formulation, charcterization and evaluation,international journal of pharma and bio sciences 1(2), 2010, www.ijpbs.net pharmaceutics.
3. Banshraj et., al a review on nanosuspensions in drug delivery, ijppr july 2013, 4(3),898-904.
4.Rajashri r. Kulkarni et al., a novel approach towards nanosuspension, ajpres, 2015,5(4)
5. Nagare sk, a review on: nanosuspensions - an innovative acceptable approach in novel delivery system, indian journal of novel drug delivery ijndd 4(3), jul-sep, 2012, 189-201.
6. N arunkumar et al., nanosuspension technology and its applications in drug delivery, asian journal of pharmaceutics, july-september 2009, 168-173
7. Debjit bhowmik et al., nanosuspension -a novel approaches in drug Delivery system, 2013, the pharmajournal 1(12), 50-63.
8. Paun j.s.et al., nanosuspension: an emerging trend for bioavailability enhancement of
Poorly soluble drugs, asian j. Pharm. Tech. 2012;2(4) , 157-168.
9. Roya yadollahi et al., nanosuspension technologies for delivery of poorly soluble drugs, journal of nanomaterials 2014.
10. Anuradha k. Gajjar et al., drug solubility: importance and enhancement techniques, 2012, isrn pharmaceutics.
11. Rashmi sharma, nanoparticle technology: formulating poorly water-soluble compounds: a review, ijpsr, 2015.
12. Ansel's pharmaceutical dosage forms and drug delivery systems by loyd allen,447-448
13. Avinash kumar reddy, nanosuspensions: ideal approach for the drug delivery of poorly
Water soluble drugs, scholar's research library, 2011, 3(2): 203-213
14. Subramanyam c.v.s., second edition, "suspensions" text book of physical pharamaceutics, pageno. 374-387.
15.ansel c., allen l.v., popovich n.g. Eighth edition "disperse systems" pharmaceutical dosage forms & drug delivery systems, lippincott williams and wilkins, philadelphia 2005, page no. Page no. 387-389, 398.
16. Harshil m. Patel1et al., nanosuspension: a novel approch to enhance solubility of poorly water soluble drugs - a review , international journal of advances in pharmaceutics ijap 5(2),2016, 21-29.
17. G geetha et.al, various techniques for preparation of nanosuspension- a review, International journal of pharma research & review, sept 2014; 3(9):30-37
18. Vishal r. Patel et al., nanosuspension: an approach to enhance solubility of drugs, j adv pharm technol res. 2011 apr-jun; 2(2): 81–87.
19. Hans de waard et al., bottom-up preparation techniques for nanocrystals of lipophilic drugs pharm res. 2011 may; 28(5): 1220–1223.
20. Rajashri r. Kulkarniet al, a novel approach towards nanosuspension asian j. Pharm. Res. 2015; vol. 5: issue 4, pg 186-194.
21. Chaudhari shilpa p et.al, nanosuspension -a novel approaches in drug delivery system, international journal of pharma research & review, dec 2013; 2(12):30-39.
22. Deoli mukesh ,nanosuspension technology for solubilizing poorly soluble drugs, int. J. Drug dev.& res., october-december 2012, 4(4): 40-49.
23. Kumar bishwajit sutradhar et al,.increasing possibilities of nanosuspension, journal of nanotechnology, 2013
24. Sneha b garasiyaet al., nanosuspension: an attempt to enhance ,bioavailability of poorly soluble drugs, ijapbc – vol. 1(1), jan- mar, 2012, 91-99.
25. Vishvajit a. Kamble etal., nanosuspension a novel drug delivery system , international journal of pharma and bio sciences oct-dec.2010 ,1(4),352-360.
26. Akshay kothawade et al., nanosuspensions: a promising drug delivery system ,journal of advanced drug delivery (jadd) ,sep- oct -2016 ,3(4),15-22.
27. Ch.prabhakar et al., a review on nanosuspensions in drug delivery, international journal of pharma and bio sciences, jan-mar-2011, 2(1), 549-558.
28. Jian zhong et al., dosage form developments of nanosuspension drug delivery system for oral administration route, current pharmaceutical design, 2015, 21, 1-11.