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# Nanosuspension: A Promising Drug Delivery System for Poorly Water Soluble Drug and Enhanced Bioavailability

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**ABSTRACT**

Nanosuspension contains submicron colloidal dispersion of pharmaceutical active ingredient particle in liquid phase which is stabilized by surfactant. Poorly water solubility is a major problem for the manufacturing of formulation. The reduction in drug particle leads to improve the bioavailability as well increase the surface area. Nanosuspension prepared by various methods. Techniques such as media milling, high-pressure homogenization have been used commercially for producing Nanosuspension. Recently engineering of nanosuspension employs emulsion and microemulsion as a templet. The unique feature of Nanosuspension has enabled their use in different dosage form and delivered by various routes such as oral, pulmonary, ocular, topical and mucoadhesive hydrogel.

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## INTRODUCTION

A Pharmaceutical Nanosuspension is a biphasic liquid system in which insoluble solid drug particles are uniformly dispersed in an aqueous vehicle. The dosage form is colloidal in nature and usually stabilized by surfactant and polymers. Nanosuspension can be administration through various routes like oral, parenteral, topical, nasal, ocular [1] so on. Bioavailability is enhanced when the particle size reduces with increase in the surface area and hence increase the rate of dissolution rate. The particle size range should be in between 200 to 600nm. Nanosized particle can increase solution velocity. More than 40% drugs are poorly water insoluble so, they show problem in formulating them in conventional dosage form [2]. Also, BCS Class 2 drugs which are poorly soluble in aqueous and organic media, the problem is much complex. In this case, lipidic nanosuspension is used as approach. It is most suitable for high log P Value and high melting point [2]. Nanosuspension prevents the existence of various concentration gradients and Ostwald ripening effect. Ostwald ripening is responsible for crystal growth. As a result, the rate of flooding of active compound increase and the plasma level reached faster (parenteral route).[3] This is one of the excellent advantages of enhancing solubility. Nanosuspension not only solves the problem but also alters the pharmacokinetics of drug and improves the drug safety and efficacy. [4]

## ADVANTAGES [5]:

- ✓ Only poorly soluble drug can be applied.
- ✓ Rapid dissolution and tissue targeting can be achieved by IV Route.
- ✓ Reduced tissue irritation.
- ✓ Improvement in biological performance due to higher dissolution rate and saturation solubility of drug.
- ✓ Long term physical stability in presence of stabilizer.
- ✓ Higher bioavailability in case of ocular administration and inhalation drug delivery.
- ✓ Nanosuspension can be incorporated into cream, gel, pellet, capsule and tablet.

**Formulation aspects of Nanosuspension:**[6,7,8,9,10,11]

**Stabilizer**

Stabilizer plays an important role in formulation of nanosuspension. In the absence of stabilizer, high surface energy of nanosized particle can produce agglomeration. The main function of stabilizer is to wet the drug particle through and to prevent Ostwald ripening. In some case, mixture of stabilizer is required to obtain a stable nanosuspension. [7]

Example - Lecithin, PVP K30, SLS, Poloxamer, cellulosic and povidone.

**Organic Solvent**

Pharmaceutically less hazardous solvent used for the Nanosuspension formulation. [8]

Example -Ethanol, methanol, isopropanol, ethyl acetate etc.

**Surfactants**

Surfactant is used to improve the dispersion by reducing the interfacial tension. They act as wetting or foaming agent. [8]

Example - Tween-80 or Span

**Co-surfactant**

It is used for influence phase behaviour when microemulsion is used to formulate the nanosuspension. Since co- surfactant can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. [9]

Example - Ethanol, glycofurol, bile salt, Transcutol. [10, 11]

**Other Additives**

According to need of required route or the property of drug. [8]

Example - Buffer, Salt, Osmogen etc.

## FORMULATION ASPECTS OF NANOSUSPENSION [4]:

**Table 1: Formulation aspects of nanosuspension**

| Excipient | Function | Example |
|---|---|---|
| Stabilizer | Wet the drug particle, prevent Ostwald ripening | Poloxamer, povidone, lecithin |
| Co-surfactant | Influence phase behaviour when microemulsion are used to formulate. nanosuspension | Bile salt, ethanol, isopropanol, glycofurol |
| Organic solvent | Less hazardous organic solvent used for nanosuspension. | Ethanol, acetone, methanol, |
| Other additive | According to need of the route of administration | Buffer, salt, polyols, osmogens |

## METHOD OF PREPARATION OF NANOSUSPENSION [12] :

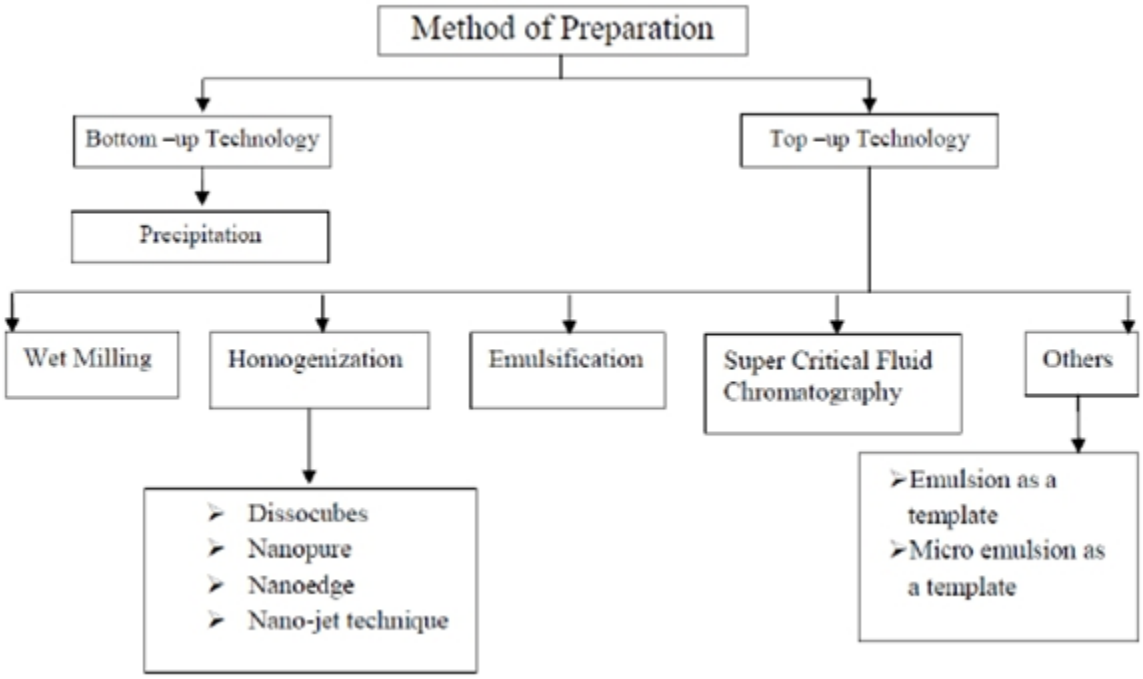


**Chart 1: Method of Preparation**

**(A) Top-down Technology:**

Top-down technology is the disintegration method. It's preferred over the precipitation method. Top-down technology includes media milling (nanocrystal), high pressure homogenization in water (disso cubes), high pressure homogenization in non-aqueous media (nanopure), combination of both precipitation and high pressure homogenization method (Nanoedge). [7, 13]

**Media Milling Techniques:**

Media milling is used to prepare nanosuspension [14]. Nanosuspension prepared by the dry milling method. Nanosuspension is produced by high shear media mills or pearl mills. The mill consists of milling chamber, milling shaft and recirculation chamber. An aqueous suspension of drug is then fed into a mill containing small grinding pearls. This pearl rotate at high speed shear rate under controlled temperature, then fly through grinding jar interior and impact against sample on opposite grinding jar wall. The combined force of friction and impact produces high degree of particle size reduction. The media milling is made of zirconium oxide or ceramic sintered aluminum oxide with high abrasion resistance. High energy and shear provide the necessary energy input disintegrate the microparticle drug into nanosized particle in media milling method, milling chamber charged with media milling, water, suitable buffer, stabilizer, and drug. Then the milling media or pearl is rotated at very high speed. The major problem concern with it that the residue of media milling remaining in the finish product could be problematic for administration. [15]

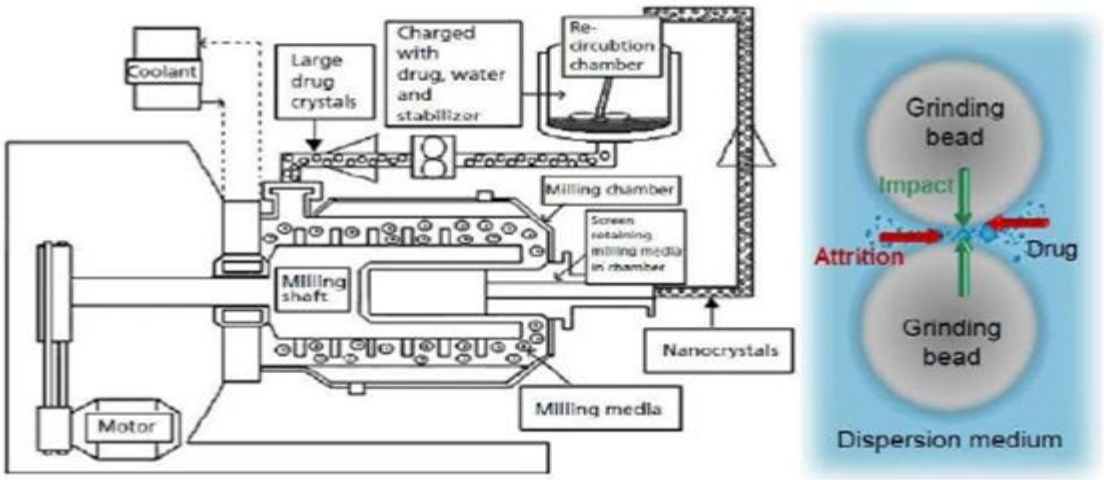


**Figure 1: Media milling technique**

**Advantage:**

- ✓ Both dilute as well as concentrated nanosuspension can be prepared.
- ✓ Nanonized distribution of final nanosized particle.

**Disadvantage:**

- ✓ Ball residues will be present as contamination in the final product.
- ✓ More time consuming.

**High pressure homogenization:**

It is used for preparing poorly water soluble drugs. In this method, the surfactant and drug is focussed under pressure and it's through nanosized aperture value of high pressure homogenizer. Principle is based on cavitations in aqueous phase. Particle cavitations force is sufficiently high to convert the drug microparticle into nanoparticle. The concern with this method is needed to small sample particle before loading and fact that many cycles of homogenization required. Disso cube technology is an example of this technology developed by R.H.Muller. [6]

**ADVANTAGE:**

- ✓ Useful for formation of very dilute as well as highly concentrate nanosuspension aseptic production scale.
- ✓ Low risk of product contamination.
- ✓ Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspension.

**DISADVANTAGE:**

- ✓ Prerequisite of micronized drug particle.
- ✓ Prerequisite of suspension formation using high speed mixture before subjecting it to homogenization.

**Dry co-grinding:**

Preparing a stable nanosuspension using dry-grinding of poorly soluble drug with soluble polymer and copolymer after dispersing in liquid media has been reported. Formation of very poorly

soluble drug such as nifedipine, griseofulvin obtained by grinding with PVP and sodium dodecyl sulphate. [16] Many soluble polymers and co-polymers such as PVP, PEG, HPMC used. Physicochemical property and dissolution of poorly soluble drug were improved by co-grinding because of an enhancement in surface polarity and transformation from crystalline to an amorphous drug. Dry co-grinding can be carried out easily and carried out without organic solvent. It reduces the particle size. [17]

**Nanoedge technology (combined precipitation and homogenization) :**

It involves the precipitation of friable material for subsequent fragmentation under condition of high shear thermal energy. This also includes the combination of rapid precipitation and high pressure homogenization. In this technique, the precipitated suspension is further homogenized to get smaller particle size and avoid crystal growth. It produces nanosized stable dispersion with short period of time**.** [18]

**Nanojet technology:**

In this method, precipitation nanosuspension is further homogenized to get smaller particle size and avoid crystal growth is performed in water using water miscible solvent as methanol, ethanol. It is desired to remove the solvent completely by including evaporation step by step a solvent free modified starting material followed by HPH. Emulsion as templet apart from the use of emulsion as drug delivery vehicle, they can also be used as nanosuspension. The use of emulsion as templet is applicable for drug which is either volatile organic solvent or partially water miscible solvent. [19]

**ADVANTAGE:**

- ✓ Particle size can easily be controlled by controlling the size.
- ✓ Easy to scale up process.
- ✓ Specialized instrument not necessary.

**DISADVANTAGE:**

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

- ✓ High amount of stabilizer required.
- ✓ Safety concern because of the use of hazardous solvent in the process.

**(B) Bottom-up Technology:**

**Nanoprecipitation method:**

The most common method of precipitation used in anti-solvent addition method in which drug is dissolved in suitable organic solvent and this solution mixed with a miscible anti-solvent. Nanoprecipitation has been coupled with high shear processing. The Nanoedge process is reliable on precipitation of material for fragmentation under condition of high shear of thermal energy. Rapid addition of a drug solution to a solvent leads to sudden saturation of the mixed solution, and generation of fine crystalline solid. [20]

**ADVANTAGE:**

- ✓ Simple process
- ✓ Ease of scale up
- ✓ Low cost equipment

**DISADVANTAGE:**

- ✓ Drug is soluble in at least one solvent and this solvent needs to be miscible of non- solvent.
- ✓ Growing of drug crystal needs to be limited by surfactant addition.

**Supercritical fluid process:**

Novel nanosizing and solubilising technology whose application is increased. Particle size reduces via supercritical fluid process. It can be defined as dense non condensable fluid. This fluid is whose temp. and pressure is greater than its critical temperature and critical pressure. Its processes allow micronization of drug particle within narrow range of particle size, often submicron level. Current SCF process has demonstrated the ability to create nanoparticulate. Nanosuspension occurs particle size between 5 to 2000nm in a diameter. Poorly soluble drug and surfactant in supercritical $CO_2$ and high pressure requires for these processes, restrict the utility of technology in industry. [21, 22]

**ADVANTAGE:**

- ✓ High drug solubilisation

**DISADVANTAGE:**

- ✓ Compound require solubility in SCF
- ✓ No easy process

**Emulsification-solvent evaporation technique:** [23]

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is non solvent for drug, evaporation of the solvent lead to precipitation of drug. Crystal growth and particle aggregation can be controlled by creating high shear force using a high speed stirrer.

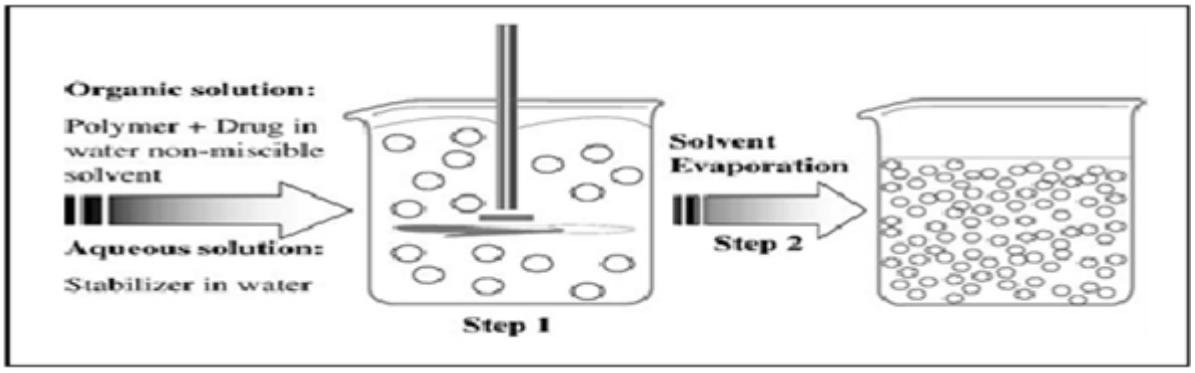


**Figure 2: Emulsification-solvent evaporation technique**

**Table 2: Summery of Nanosuspension formation technology and compound produced in nanosuspension [3]:**

| Technology | Advantage | Disadvantage | Drug |
|---|---|---|---|
| Precipitation | -simple process<br>-low cost equipment<br>-easy to scale up | -drug has to soluble in at least one solvent and that is need to be miscible with a non solvent.<br>-growing of drug crystal need to be limit by surfactant addition. | Carbamazepine<br>Cyclosporine<br>Retinoic acid |
| High pressure homogenization | -general applicability to most drug.<br>-Used for formation of very dilute as well as highly conc. nanosuspension<br>-low risk of product contamination. | -high number of homogenization cycle<br>-possible contamination occur from metal ion coming off from the wall of the homogenizer | Albendazole<br>Amphotericin B<br>Clofazamine<br>Azithromycin<br>Fenofibrate |
| Emulsion templet | -high drug solubilisation<br>-long shelf life<br>-ease of manufacture | -use of hazardous solvent<br>Use of high amount of surfactant and stabilizer | -ibuprofen<br>Mitotane |
| Media milling | -easy to scale up<br>-little batch to batch variation<br>High flexibility to handling large quantities of drug | -generation of residue of media milling<br>Require milling process to hours to days<br>-prolong milling may induce the formation of amorphous lead to instability | Cilostazol<br>Naproxen |
| Dry co-grinding | -easy process<br>-no organic solvent<br>-require short grinding time | -generation of residue of media milling | Clarithromycin<br>Glibenclamide<br>Naproxen<br>Phenytoin |

## CHARACTERIZATION AND EVALUATION PARAMETER: [24]

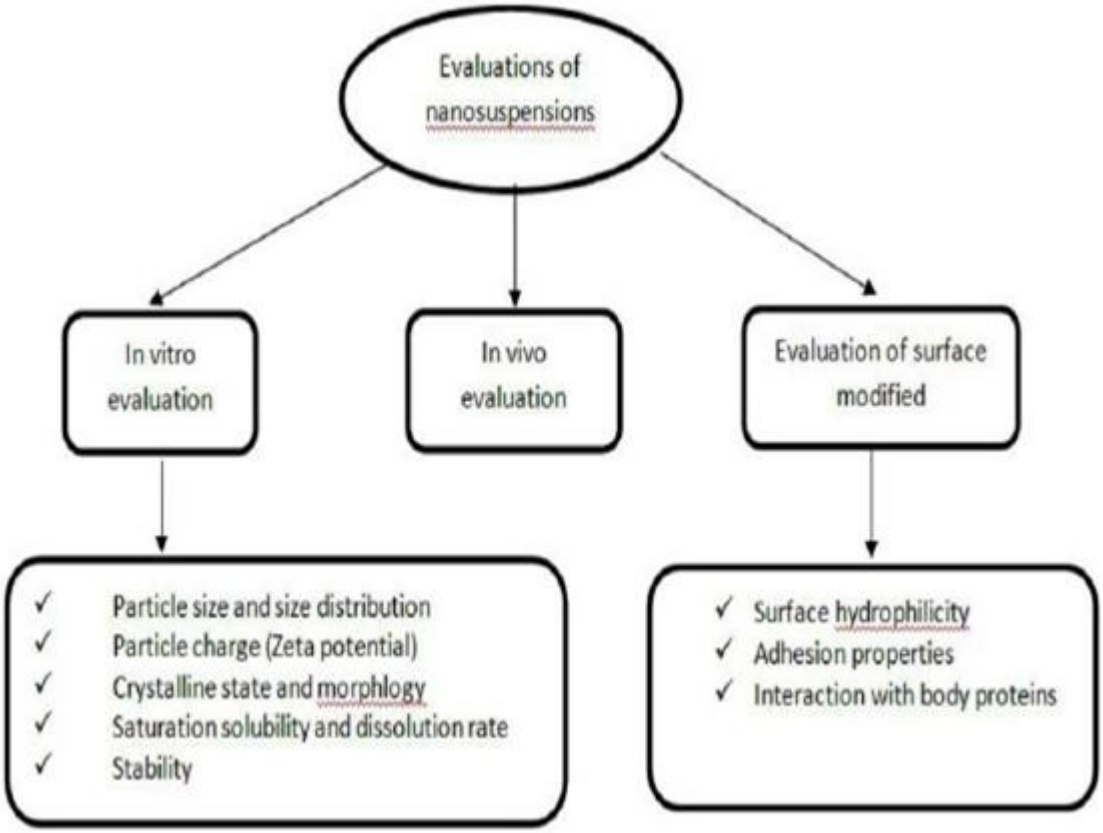


**Chart 2: Characterization and Evaluation Parameter**

### *In-vitro* Evaluation Parameter :

### 1. Particle Size Distribution: [25,26]

The most important characterization parameter which is determined the mean particle size and the width of particle size distribution called as polydispersity index. It is determined Photon Correlation Spectroscopy (PCS). Particle size and Polydispersity Index (PI) govern saturated solubility, dissolution velocity and biological performance. Various technique for determining particle size distribution which are PCS, laser diffraction (LD), and coulter counter multisizer. PCS can even be used for determining the width of particle size distribution in range of 3nm to 3mcm. LD measures volume size distribution and measures particle size ranging from 0.05-80mcm up to 2000mcm.

### 2. Particle charge (zeta potential) [24]:

Particle charge examined the stability of nanosuspension.

Electrostatically stabilize nanosuspension a minimum zeta potential of ±30 mV. And for combined stearic and electrostatic stabilization, it should be minimum of Mean ±20 mV.

**3. Crystalline state and particle morphology [24]:**

Crystalline structure is determined by the differential scanning colorimeter. While nanosuspension is prepared from drug particle and get to convert into amorphous form. Hence, it is essential to measure the extent of amorphous drug generated during the production of nanosuspension.

X-ray diffraction (XRD) is also used for the examining change in physical state and extent of amorphous drug. It is most important for the crystal morphology. It gives the information about the change in physical state of drug particle as well as extent of the amorphous fraction.

Scanning electron microscopy is also used to get accurate information about particle size morphology.

**4. Saturation solubility and Dissolution velocity [24]:**

Nanosuspension increases the saturation solubility as well as dissolution velocity. Saturation solubility is depending upon the temperature and properties of dissolution medium. Kelvin equation and Ostwald- freundlitch equation can explain increase in saturation solubility.

**5. Stability [24]:**

Nanosuspension stability depends on particle size and suspended particles. Reduce the particle size to the nano range, increase the surface energy of the particle and then tendency of particle agglomerate increases. So the stabilizer is used to prevent Ostwald ripening effect. Stabilizer like lecithin, Poloxamer, polysorbates and Povidones are generally used in nanosuspension.

**6. Osmolarity[24]:**

Measured by using osmometer.

**7. pH [24]:**

Prepared nanosuspension was taken in beaker and measured by using pH meter:

***In-vivo* Evaluation [27]:**

Particular drug and route of administration need the specific *in vivo* evaluation of the nanosuspension. For intravenously injected nanosuspension, the organ distribution in part depends on the nanoparticle size and surface property. Plasma drug concentration is determined by HPLC-UV-visible spectroscopy. Surface Hydrophobicity/hydrophilicity and interaction with body proteins are generally evaluated by *in-vivo* parameter. Surface Hydrophobicity is evaluated by hydrophobic interaction chromatography and absorption of protein is determined by 2-D PAGE quantitative measurement after intravenous injection of nanosuspension of drug in animals.

**Application of Nanosuspension:**

**1. Target drug delivery:**

Nanosuspension can be used for the targeted delivery as their surface property *in vivo* behavior can easily be altered by changing either stabilizer. Nanosuspension by using various surface coating for active or passive targeting of the desired site is the future of targeted drug delivery system. Targeting of *Cryptosporidium partum,* the organism responsible for the cryptosporidiosis, was obtained by using surface modified mucoadhesive nanosuspension bupravaquone**.** [28]

**2. Oral drug delivery:**

Oral route for drug delivery has well-known advantage. Orally administrative antibiotic such as atovaquone reflect this problem well. Nanosizing of such drug leads to dramatic increase in their oral absorption and bioavailability respectively. [29]

**3. Ocular drug delivery:**

Nanosuspension could be proven to be vital for drug that exhibit poor solubility in lachrymal fluid.[30] Suspension offer most advantage such as prolong resistance in cul-de-sac, which is desired the most ocular disease for effective treatment. To improve the saturation solubility of drug, represent ideally approach to ophthalmic delivery of hydrophobic drug. Example, polymeric nanosuspension of ibuprofen, prepared using eudragit RS100 by a quasi-emulsion and solvent diffusion method. [31]

**4. Topical formulation:**

Drug nanoparticle can be incorporated into cream or water free ointment. The nanocrystal from leads to increase saturation solubility of the drug in topical dosage form, thus enhancing the diffusion of the drug into the skin. [32]

**5. Parenteral drug delivery:**

Nanosuspension can be administered via distinctive route ranging from intra-articular via intraperitoneal to intravenous injection. Recently approach for parenteral drug delivery includes solubilization, salt formation using co-solvent, micelles solution, and complexation with cyclodextrin or current liposome. In addition nanosuspension found to increase the efficacy of parental administration of drug. Hence, nanosuspension enable significant to improve in the parenterally tolerable dose of drug/lead to reduce cost of therapy and also enhance the therapeutic performance. Nanosuspension has been found to increase the efficacy of parenterally administered drug. Paclitaxel nanosuspension revealed their superiority over taxol in reducing the median tumor burden. [33]

**Marketed Formulation of Nanosuspension:**

**Table: 3 New drug application based on nanosuspension technique reported and marketed by now** [3]

| Drugs | Indication | Route | Author or company name | Status |
|---|---|---|---|---|
| Paclitaxel | Anticancer | Intravenous | American bioscience | Marketed |
| Naproxen | Anti-inflammatory | Oral/parental | Anchalee ain-ai | Reporeted |
| Fenofibrate | Lipid lowering | Oral | Skyepharma | Marketed |
| Silver | Eczema | Topical | NUCRYST | Phase3 |
| Omeprazole | Proton pump inhibitor | Intravenous | Jan-ichi jinno | Reported |
| Ketoprofen | Analgesic | Oral | M.A.Kassem | Reported |
| Prednisolone | Glucocorticoid | Ophthalmic | M.A.Kassem | Reported |

**Advantage of Nanosuspension over conventional formulation:** [34]

**Table 4: Advantage of nanosuspension over conventional formulation:**

| Route of administration | Disadvantage of conventional formulation | Benefits of nanosuspension |
|---|---|---|
| Oral | Slow onset of action | Rapid onset of action |
| Ocular | Lachrymal wash off/low bioavailability | Higher bioavailability |
| Intravenous | Poor dissolution | Rapid dissolution |
| Intramuscular | Low patient compliance due to pain | Reduced skin irritation |
| Inhalation | Low bioavailability due to solubility | Rapid dissolution/high bioavailability. |
| Topical | Skin irritation produced/redness/low permeation | Reduced skin irritation/high permeation. |

## CONCLUSION

The nanosuspension technology can be successfully utilized for overcoming problem associated poorly soluble drugs or lipophilic drugs insoluble in both organic and aqueous media. Large scale production of nanosuspension can be employed by media milling and high pressure homogenization technique. The recent advancement in the work being done related to nanosuspension shows that many formulations are being developed on a laboratory scale which have a potentially important clinical significant and can be used for the mitigation of disease.

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