



## NANOSUSPENSION OF A DRUG AND ITS BIOLOGICAL ACTIVITY- A REVIEW

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### ABSTRACT

With the modern technologies, a large number of drugs have been discovered which have better efficiency but their clinical applications are restricted due to poor solubility. Nearly 40% of the drugs have poor solubility. Poor water solubility has become a leading challenge for formulation of these compounds. Poor solubility is generally associated with poor bioavailability. Nanosuspension has the potential to overcome this issue. This review article outlines various techniques involved for preparation of nanosuspension and the enhancement of biological activities of drug when formulated into nanosuspension.

**Key words:** Nanosuspension, Solubility of drug, Dissolution rate.

### INTRODUCTION

More than 40% of new chemical entities are lipophilic compounds. Lipophilic compounds have poor aqueous solubility and imperfect dissolution profile which causes their low bioavailability. Therefore, formulating new poorly water soluble molecules to obtain an adequate bioavailability has become a serious and challenging scientific, industrial, and medical issue. To overcome these problems Nanotechnology can be used. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is  $10^{-9}$  m [1]. Nanosuspension is a submicron colloidal dispersion of drug particles which are stabilized by surfactants. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral or topical use or for parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 to 600 nm [2].

### Advantages

- Most cost effective.
- Useful for poorly soluble drugs.
- Physically more stable than liposomes.
- Provide ease of manufacture and scale up for large scale production.
- Rapid dissolution and tissue targeting.

- Reduction in tissue irritation.
- Higher bioavailability in ocular and inhalational drug delivery [3].

### PREPARATION TECHNIQUES

Techniques of preparation are classified into 2 types

- Top Down process
  - ✓ Media Milling
  - ✓ High pressure homogenisation
- Bottom up process
  - ✓ spray freezing
  - ✓ evaporative precipitation
  - ✓ liquid solvent change process

### MEDIA MILLING TECHNIQUE

The media milling technique was developed by Liversidge et al. In this method high-shear media mills or pearl mills are used to produce nanosuspension. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber. The milling media or balls are framed in ceramic-sintered aluminium oxide or highly cross-linked polystyrene resin. The milling chamber is fed with an aqueous suspension of the drug, stabilizer, and the milling media or pearls rotate at a very high shear rate. This procedure can be carried out under controlled

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temperature. The friction and collisions among drug particles and pearls generate nanosuspension [4].

### **HIGH PRESSURE HOMOGENISATION TECHNIQUE**

In this technique suspension is forced by a pressure plunger pump through a narrow valve under high pressure. When the suspension is allowed to pass through the orifice the static pressure will be reduced below the boiling pressure of water which results in the boiling of water and formation of gas bubbles. When it leaves the orifice pressure will be normal and bubbles will implode. So surrounding particles will rush into the surface which causes the size reduction. This principle is employed in the Avigauin micron lab 40 homogenizer [5].

### **BIOLOGICAL ACTIVITIES OF NANO SUSPENSIONS**

Antifungal agents such as Miconazole, Fluconazole, Ketoconazole, Posaconazole clinical efficacy is well established, the potency is decreased by thousand fold when reaches the target site, and also large dose and/or prolonged administration is often necessary to maintain an effective drug concentration. The long-term use of systemic antifungal drugs is associated with potential adverse effects and patient non-compliance and also less drug availability at the site of infection, limits its use. So when they were formulated as nanosuspension it will reduce the dose and increase the concentration of drug in the targeted organ with low systemic concentration is highly desirable [6-8]

Ciprofloxacin is a broad spectrum second generation fluoroquinolone antibiotic which is effective against gram positive and gram negative bacteria. It kills bacteria by interfering with topoisomerase which stops synthesis of DNA and of protein. It is practically insoluble in water and sensitive to sunlight losing its antibacterial activity. Ciprofloxacin solubility enhancement is achieved by using a classical cyclodextrin inclusion complex and a current nanotechnology approach. Inclusion complexes were prepared with beta-cyclodextrin using kneading method. Nanosuspension of ciprofloxacin was prepared by anti solvent precipitation method. Pure ciprofloxacin suspension and equivalent amount of nano-suspension and inclusion complexes were tested and compared for antibacterial activity using agar diffusion method against gram positive bacteria such as MRSA ATCC # 33591, *B. subtilis* ATCC # 10400, *E. coli* ATCC # 13706, *K. pneumoniae* ATCC # 13368, *P. aeruginosa* ATCC # 27853. Observed zone of inhibition by all treatment were statistically analyzed by measuring zone of inhibition. And thus better Antibacterial activities were found for Ciprofloxacin beta cyclodextrin complexes and its nanosuspension than pure ciprofloxacin nanosuspension [9].

Curcumin is a natural product found in the rhizome of *Curcuma longa*. It has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, anticancer activities and has a potential against various malignant diseases, diabetes, allergies, arthritis,

alzheimer's disease etc. Nanosuspension of Curcumin was prepared by bottom up method using acetone and water as solvent system. Curcumin is a poorly soluble drug. In order to increase its solubility, bioavailability, stability Curcumin was formulated as Nanosuspension [10].

Cyclosporine A, a neutral hydrophobic cyclic peptide composed of 11 amino acid residues, is a 3rd generation immunosuppressant, used in organ transplantation. The aqueous solubility of CsA is very low and it displays a considerable inter and intra patient variability presumably due to its poor and highly bile dependent absorption as well as intestinal metabolism. Hence therapy requires careful monitoring of blood levels. Exceeding the therapeutic window adverse effects like nephrotoxicity and hepatotoxicity are reported. Furthermore it has been reported that at sub therapeutic drug levels, organ transplantation rejection occurs after systemic drug administration in case of lung, heart, lung or corneal transplantation. A stable nanosuspension of cyclosporine A using Zirconium oxide beads was prepared by Media milling technique. Nanosuspension formulation containing Cyclosporine A can be an alternative dosage form of intravenous microemulsion formulation by avoiding a hypersensitivity reaction caused by Cremophore EL. All Pharmacokinetic parameters show favorable results. It can modulate the disposition of drug in the body and potentially improve the safety & efficacy profile of drug. It is a simple, cost effective and scalable method as compared to other methods [11].

Felodipine is, a dihydropyridine calcium antagonist, widely used as a potent antihypertensive drug. It is poorly soluble and oral bioavailability is only 15%. Its dissolution profile is the limiting factor of its bioavailability. In order to increase its dissolution rate several attempts were carried out. Out of these Nanosuspensions by the virtue of their large surface area to volume ratio provide an alternative method to formulate poorly soluble compounds. Felodipine nanosuspension were prepared by precipitation-ultra sonication technique using ethanol as solvent and aqueous medium containing stabiliser as anti solvent. Poly Vinyl alcohol or Hydroxy propyl methyl cellulose was used as stabiliser. Nanosuspension showed enhanced drug release which may lead to enhanced oral bioavailability of felodipine. Since the limited oral bioavailability of felodipine is due to its poor dissolution, hence, the increase solubility and thereby the dissolution of felodipine in the form of nanosuspension may enhance the oral bioavailability of felodipine [12].

Nebivolol hydrochloride is a poorly water soluble drug falls under class II biopharmaceutical classification system, which is  $\beta_1$  receptor antagonist that leads to vasodilatation, decreased peripheral vascular resistance, lowers blood pressure and heart rate. The rate of its oral absorption is often controlled by dissolution rate in the gastro intestinal tract. Nanosuspension tablets changes the properties of poorly soluble drugs like nebigolol hydrochloride and increases the wetting property and surface area of the drug particle and indirectly increases the dissolution and oral bioavailability of drugs. The nanosuspension tablets shown higher dissolution rate

compare to the innovator product and pure drug. Nanosuspension tablets are promising alternative technique for improving dissolution rate and bioavailability of drugs [13].

Nisoldipine is an antihypertensive drug with poor water solubility, high permeability and it belongs to Class II of Bio pharmaceutical classification system (BCS). The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) class II and IV to increase their solubility. Nanosuspension of Nisoldipine was prepared by Nanoprecipitation method. Nanosuspension OF Nisoldipine represent a promising alternative to current drug delivery systems aiming to improve the biopharmaceutical performance such as solubility and bioavailability [14].

Azithromycin is a drug which is classified as a BCS class II substance, since it has low aqueous solubility and high permeability. Low solubility contributes to high variability in absorption after oral administration. Once the solubility problem is overcome azithromycin will be absorbed immediately showing comparatively good oral bioavailability. Therefore to overcome this problem the solubility of the drug has to be enhanced because the faster the drug dissolved, faster will it absorb and hence the pharmacological action be attained. Hence to overcome this problem nanosuspension technology is used [15].

In ocular drug delivery system, ocular infections are treated by various topical drug applications in the form of solutions, suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability due to minimum ocular residence time, because of various anatomical and pathophysiological barriers prevailing in the eye. To overcome these problems its formulated as Nanosuspension. Nanosuspension not only improves the saturation solubility of drug in media but it is also ideal approach for ophthalmic delivery of hydrophobic drugs in eye. Nanosuspensions can also used to achieve sustained release of the drug by incorporating or formulating with suitable hydrogel or mucoadhesive base or in ocular inserts [16].

Simvastatin is a lipid lowering agent and is an inhibitor of 3-hydroxy -3- methyl glutaryl co - enzyme

A(HMG Co A) Reductase. Simvastatin is white, crystalline and insoluble in water. To overcome the problems of low solubility Simvastatin were formulated as nanosuspension. Nanosuspension was prepared by Emulsification solvent diffusion method [17].

Candesartan,  $(\pm)$ 1-[[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H tetrazol-5-yl)- biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate, a non-peptide, is a selective AT1 subtype angiotensin II receptor antagonist indicated for the treatment of hypertension alone or in combination with other antihypertensive agents . Candesartan cilexetil is a pro-drug that is hydrolyzed to candesartan during absorption from the gastrointestinal tract. The aqueous solubility of Candesartan cilexetil is less than  $5 \times 10^{-5}$  g/L which may be the reason for very low bioavailability. The results of the pharmacodynamic study showed significant reduction in blood pressure for nanosuspension as compare to plain drug suspension. Thus, the results of the *in vitro* and pharmacodynamic studies conclusively demonstrated significant enhancement in antihypertensive activity of candesartan when formulated as nanosuspension. NS was prepared by media milling technique using zirconium oxide beads as milling media [18].

Valsartan is an AngiotensinII antagonist that is selective for type I(AT1) angiotensin receptor. Valsartan is mainly used for the treatment of high blood pressure, congestive heart failure. High pressure homogenization method was developed to prepare Valsartan nanosuspension using poloxamer and soyalecithin as stabilizers. From the results of this study it may be concluded that nanosuspensions of poorly soluble drugs such as Valsartan are easy to prepare and represent a promising new drug formulation for oral controlled drug delivery for treatment of Hypertension [19].

Nateglinide is one of the most effective drug in the treatment of diabetics. It is BCS class II drug with low solubility. Nateglinide is non-sulfonyl urea drug which blocks KATP potassium channel to perform overall glycemic control in type2 diabetics. It is selective blocker of pancreatic beta cells. Nateglinide nanosuspension was formulated by nanoprecipitation method. The formulated nanosuspension shows good solubility and bioavailability and thus can be therapeutically superior to all conventional formulations [20].

**Table 1. Advantages and Disadvantages Of Different Methods**

Technology	Advantage	Disadvantage
Precipitation [6]	<ul style="list-style-type: none"> <li>Finely dispersed drug</li> <li>Good control of desired size</li> </ul>	<ul style="list-style-type: none"> <li>Needs to be stabilized</li> <li>Organic solvent residues</li> <li>Not universally applicable</li> </ul>
Milling [6]	<ul style="list-style-type: none"> <li>Low energy technique</li> <li>Proven by FDA</li> </ul>	<ul style="list-style-type: none"> <li>Residue from milling process</li> <li>Needs to be stabilized</li> <li>Can be a slow process</li> </ul>
Homogenization [7]	<ul style="list-style-type: none"> <li>Universally applicable</li> <li>No problem with large batches</li> <li>Fast method</li> </ul>	<ul style="list-style-type: none"> <li>High energy technique</li> <li>Great experience needed</li> </ul>

## CONCLUSION

Numbers of drug candidates are identified in drug discovery programs, but most of them are poorly soluble. Therefore nanoformulation can improve the solubility as well as dissolution rate and also enhances its biological activities.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.