



## NANOSUSPENSIONS TECHNOLOGY IN DRUG DELIVERY – A REVIEW

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### ABSTRACT

Nanosuspensions is colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1  $\mu\text{m}$  in size. 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. This review focused on unique advantages of Nanosuspensions, which 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. Nanosuspensions differ from Nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nanoparticles (SLN), which are lipidic carriers of drug.

**Keywords:** Nanosuspensions, Solubility, Advantages, Methods of preparation.

### INTRODUCTION

Various formulation parameters that play a crucial role in the successful formulation of drugs are aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility with solvent and excipient. Among this aqueous solubility became a hurdle for the formulation of new molecular entities. More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds. Formulating a poorly water soluble drug has always been a challenging problem confronted by the pharmaceutical scientist.

Taking this fact into concern many approaches like solid dispersions, cocrystals, microemulsions, nanocapsules, nanoparticles, solid lipid nanoparticles etc. have been adopted to improve the solubility of poorly soluble drugs. A pharmaceutical Nanosuspensions is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or 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 and 600 nm. Nanosuspensions have proved their potential to overcome the problems associated with the delivery of poorly water-soluble and poorly water and lipid soluble drugs, and their simplicity and the advantages lifted up its position over the other conventional strategies [2]. The advantages of the Nanosuspensions over current conventional deliveries were given in table 1. In Nanosuspensions technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability.

The stability of the particles obtained in the Nanosuspensions 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.

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.

## Methods of preparation of Nanosuspensions

### a. Precipitation technique

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. This is accomplished by a combination of rapid precipitation and high-pressure homogenization. The NANOEDGE patented technology US 6,884,436 by Baxter depends on the precipitation of friable materials for fragmentation under conditions of high shear and/or thermal energy [3]. Rapid addition of a

### Nanojet technology

Nanojet technology is also called as opposite stream technology. In this technique a stream of suspension in two or more divided parts were passed with high pressure were made to colloid with each other, due to the high shear forces produced during the process leads to results in the reduction of particle size.

### c. Lipid emulsion/micro-emulsion template

Lipid emulsions techniques are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique includes 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 Nanosuspensions which is stabilized by surfactants. Another way to produce Nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, micro-emulsions as templates can produce Nanosuspensions. Micro-emulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed micro-emulsion can be saturated with the drug by intimate mixing. Suitable dilution of the micro-emulsion yields the drug Nanosuspensions.

### d. Melt emulsification method

In this method drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting

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 [4].

### b. High pressure homogenization

In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation forces of drug particles in the aqueous phase. These forces are sufficiently high to convert the drug microparticles into nanoparticles [5, 6]. DissoCubes developed by R.H. Muller using a piston-gap-type high pressure homogenizer adopts this technology, which was recently released as a patent US 5,858,410 owned by SkyePharm plc [7].

point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath. The main advantage of melt emulsification technique relative to the solvent diffusion method is total avoidance of organic solvents during the production process.

### e. Milling techniques

#### i. Media milling

Media milling is a further technique used to prepare Nanosuspensions. Nanocrystal is a patent protected technology US 5,145,684 developed by Élan Nanosystems [8]. In this technique, the drug nanoparticles are obtained by subjecting the drug to media 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.

#### ii. Dry co-grinding

Recently, Nanosuspensions can be obtained by dry milling techniques [9, 10]. Dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained.

### f. Supercritical fluid method

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA). The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. The disadvantages of the above methods are use of hazardous solvents and use of high proportions of surfactants and

stabilizers as compared with other techniques, particle nucleation overgrowth due to transient high super saturation, which may also result in the development of an amorphous form or another undesired polymorph.

## Formulation concerns

### Stabilizer

The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent ostwald's ripening and agglomeration of nanosuspension in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilizer has a pronounced effect on the physical stability and in vivo behavior of nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, celluloses, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable Nanosuspensions.

### Co-surfactants

The choice of co-surfactant is critical when using microemulsions to formulate Nanosuspensions. Since co-surfactants 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. Although the literature describes the use of bile salts and dipotassium glycyrrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

### Organic solvent

The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol, ethanol, chloroform, isopropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane.

### Other additives

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

## Characterization of Nanosuspensions

According to muller's review (2001), the evaluation parameters considered for Nanosuspensions are size and size distribution, particle charge (zeta potential), crystalline status, as well as dissolution velocity and saturation solubility.

### a. Particle size distribution

The most important characterization parameter for the Nanosuspensions are the mean particle size and polydispersity index which governs the physicochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. It is proved that change in particle size changes saturated solubility and dissolution velocity. Different methods for

determining particle size distribution are photon correlation spectroscopy (PCS), laser diffraction (LD), and coulter counter multisizer. PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of Nanosuspensions and should be as low as possible for the long-term stability of Nanosuspensions. The PI value of 0.1–0.25 indicates a fairly narrow size distribution where as a PI value greater than 0.5 indicates a very broad distribution. PCS determines the particle size in the range of (3nm to 3  $\mu\text{m}$ ) it becomes difficult to determine the possibility of contamination of the Nanosuspensions by microparticulate drugs (having particle size greater than 3 $\mu\text{m}$ ).

Hence, in addition to PCS analysis, laser diffractometry (LD) analysis of Nanosuspensions should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process. LD determines the particle size in the range of 0.05-80 $\mu\text{m}$  upto 2000 $\mu\text{m}$ . For parental use the particle size should be less than 5 $\mu\text{m}$ , considering that the smaller size of the capillaries is 5-6  $\mu\text{m}$  and hence a higher particle size can lead to capillary blockade and embolism. For Nanosuspensions which are intended for intravenous administration, particle size analysis by the Coulter counter technique is essential in addition to PCS and LD analysis. Since the Coulter counter gives the absolute number of particles per volume unit for the different size classes. The Noyes–Whitney equation [11], Ostwald–Freundlich equation [12] and Kelvin equation [13] could be used to explain the relationships between particle sizes, saturation solubility.

### b. Zeta potential (particle charge distribution)

Zeta potential determines the physical stability of nanosuspension. Zeta potential is an indirect measurement of the thickness of the diffusion layer, i.e. can be used to predict long term stability. In order to obtain a Nanosuspensions exhibiting good stability, for an electrostatically stabilized Nanosuspensions a minimum zeta potential of  $\pm 30\text{mv}$  is required [14] whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of  $\pm 20\text{mV}$  is desirable.

### c. Crystal structure/ morphology

X-ray diffraction analysis in combination with differential scanning calorimetry, scanning electron microscopy is used to determine the polymorphic changes due to impact of high pressure homogenization in the crystalline structure of the drug. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization. In order to get an actual understanding of particle morphology, the techniques such as scanning electron microscopy (SEM), atomic force microscopy (AFM) or transmission electron microscopy (TEM) [15] are preferred. This reveals the exact size and morphology of nanoparticles in suspension.

**d. Saturation solubility and dissolution velocity**

Nanosuspensions increase the dissolution velocity and saturation solubility. Size reduction leads to increase in the dissolution pressure. An increase in solubility that occurs with relatively low particle size reduction may be mainly due to a change in surface tension leading to increased saturation solubility.

**e. In-Vivo Pharmacokinetic correlation**

The establishment of relationship between *in-vitro* release and *in-vivo* absorption and the monitoring of the *in-vivo* performance of the Nanosuspensions are essential to a successful preparation, irrespective of the administration route and the delivery systems. For oral Nanosuspensions, the drug dissolution rate can influence *in-vivo* biological performance of formulations to larger extent [16, 17]. For intravenously injected Nanosuspensions, the organ distribution in part depends on the nanoparticle size and surface property. Surface hydrophilicity/ hydrophobicity and interactions with plasma proteins are considered as important factors affecting the *in-vivo* organ distribution behavior after i.v. injection of Nanosuspensions. With the quick development of physical chemistry and biochemistry, many techniques to evaluate the surface properties and protein interactions have emerged recently. 2-D PAGE can be employed for the quantitative measurement of protein adsorption to nanoparticle surface after i.v. injection of drug Nanosuspensions to animals [18]. Although establishment of an *in-vitro/in-vivo* relationship is extremely important to Nanosuspensions, the biorelevant studies have not been reported by far.

**Preferred Dosage Forms of Nanosuspensions**

Aqueous or non-aqueous drug Nanosuspensions exhibiting a physical long-term stability should be sufficient to place them on the market as liquid products. In the case of drug Nanosuspensions in pure water or in water containing mixtures, they can be used as granulation fluid in the granulation process for the production of tablets or alternatively as wetting agents for the extrusion mass to produce pellets. Spray-drying of the Nanosuspensions is also possible. The produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules. The drug nanocrystals produced in non-aqueous media such as oils or liquid/solid PEG can be used directly for filling in capsules. Production of drug Nanosuspensions in melted PEG which is solid at room temperature opens further perspectives. Direct filling of capsules with the hot Nanosuspensions is possible [19]. Alternatively after solidification of the PEG, the drug nanocrystal containing mass can be ground and filled as a powder into the capsules. To summarize, there are different ways to transfer the drug nanocrystals to a final dry oral dosage form for the patient. With regard to parenteral products, the drug Nanosuspensions can be used as they are; a shelf life of up to three years was shown for selected Nanosuspensions. Alternatively, lyophilized products can be offered to be reconstituted prior to administration.

Table 1.3 summarizes current marketed Nanosuspensions formulations [20].

**Applications of Nanosuspensions in Drug Delivery****a. Parenteral administration**

Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitoneal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5  $\mu\text{m}$  to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, Nanosuspensions have been found to increase the efficacy of parenterally administered drugs.

**b. Oral administration**

Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. Aqueous Nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. The aqueous Nanosuspensions can be used directly in the granulation process or as a wetting agent for preparing the extrusion mass pellets. A similar process has been reported for incorporating solid lipid nanoparticles into pellets. Granulates can also be produced by spray drying of Nanosuspensions.

**c. Ophthalmic drug delivery**

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids.

**d. Pulmonary drug delivery**

Aqueous Nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Basically the Nanosuspensions can be used in all

nebulizers. The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles.

#### **e. Bioavailability enhancement**

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability or poor stability in the gastrointestinal tract (GIT).

Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a Nanosuspensions formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the Lyophilized Nanosuspensions powder when compared with the dissolution from a coarse powder (15% in 20 min).

#### **f. Target drug delivery**

Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable Nanosuspensions for targeted delivery.

The engineering of stealth Nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [21].

#### **g. Topical formulations**

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin [22].

#### **h. Mucoadhesion of the nanoparticles**

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." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the Nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT. Table 4 summarizes all the drugs that have been formulated as Nanosuspensions and their respective routes of administration [23].

**Table 1. Advantages of Nanosuspensions over conventional formulations**

<i>Route of administration</i>	<i>Disadvantages of conventional formulations</i>	<i>Benefits of Nanosuspensions</i>
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improved solubility so improved bioavailability
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/ non specific action	Rapid dissolution/ tissue targeting
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation
Inhalations	Low bioavailability due to low solubility	Rapid dissolution/ high bioavailability/ dose regulation

**Table 2. Advantages and disadvantages of various preparation techniques of Nanosuspensions**

<b>Method</b>	<b>Advantages</b>	<b>Disadvantages</b>
High-pressure homogenization	ease of scale-up and little batch-to-batch variation, narrow size distribution in the final product, allowing aseptic production of Nanosuspensions for parenteral administration and flexibility in handling the drug quantity	pretreatment of micronized drug particles and presuspending materials before subjecting it to homogenization
Milling	the same as those for high-pressure homogenization	potential erosion of material from the milling pearls
Microprecipitation	low need of energy, stable products and simple process	narrowly applying space, wide size distribution and potential toxicity of non-aqueous solvents
Emulsion and microemulsion	need low of energy, stable products, simple process, small size of particles and uniform particle distribution	high concentration undesired surfactants and residual solvents
Microprecipitation-high pressure homogenization	much smaller, more uniform and more stable compared to that by the microprecipitation; less mechanical force and energy compared with the high-pressure homogenization	The manufacturing process is complicated
Melt emulsification	avoidance of organic solvents compared to the solvent diffusion	Few compliant objects, larger particles from it than solvent diffusion

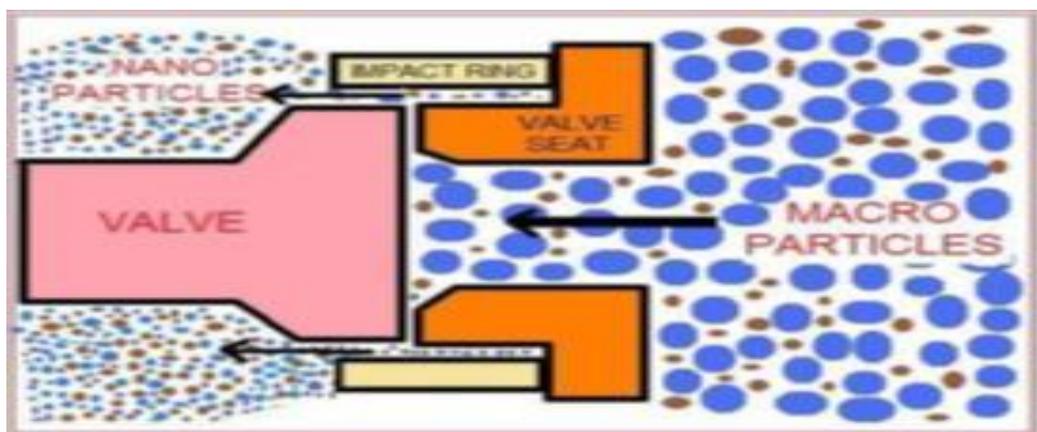
**Table 3. Current marketed formulations using Nanosuspensions technology**

Drug	Use	Company/ Individual	Preparation technology
Sirolimus (RAPAMUNE®)	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals®
Aprepitant (EMEND®)	Antiemetic	Merck	Elan Drug Delivery Nanocrystals®
Fenofibrate (TriCor®)	Treatment of hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals®
Megestrol Acetate (MEGACE® ES)	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals®
Fenofibrate (Triglide™)	Treatment of Hypercholesterolemia	First Horizon Pharmaceutical	SkyePharma IDD®-P technology

**Table 4. Application of Nanosuspensions technology for various drugs**

Drugs	Use	Company/ individual	Route of administration
Paclitaxel	Anticancer	American Bioscience	Intravenous
Danazol	Hormone	Rogers T.L.	Oral
Naproxen	Anti-inflammatory	Anchalee Ain-Ai	Oral/parenteral
Probucol	Lipid lowering	Jyutaro Shudo	Oral
Cytokine inhibitor	Crohn's disease	Elan Nanosystems	Oral
Fenofibrate	Lipid lowering	SkyePharma	Oral
Megestrol acetate	Steroid hormone	PAR Pharmaceuticals	Oral
paliperidone palmitate	Anti-schizophrenia	Johnson and Johnson	Oral
Loviride	Antivirotic	B. Van Eerdenbrugh	Intravenous
Busulfan	Anticancer	SkyePharma	Intrathecal
Budesonide	Asthma	Jerry Z. Yang	Pulmonary
Fluticasone	Asthma	Jerry Z. Yang	Pulmonary
Insulin	Diabetes	BioSante	Oral
Clofazimine	Antimycobacterials	K. Peters	Intravenous
Oridonin	Anticancer	Lei Gao	Intravenous
AZ68	Anticancer	Kalle S.	Oral/Intravenous
Ascorbyl palmitate	Antioxidant	Veerawat T.	Intravenous
Hydrocortisone	Glucocorticoid	M.A. Kassem	Ophthalmic
Prednisolone	Glucocorticoid	M.A. Kassem	Ophthalmic
Hexadecadrol	Glucocorticoid	M.A. Kassem	Ophthalmic
Aphidicolin	Antileishmanial	O. Kayser	Oral
Dihydroartemisinin	Antimalarial	Jiraporn C.	Oral
Cilostazol	Antiplatelet agent	Jun-ichi Jinno	Oral
Spironolactone	Diuretics	P. Langguth	Intravenous

**Fig 1. High Pressure Homogenization Mechanism**



## CONCLUSION

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Production techniques such as media milling and high pressure homogenizer are used for large scale production of

nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnology is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form.

## REFERENCES

1. RH Müller, C Jacobs and O Kayer. Nanosuspensions for the formulation of poorly soluble drugs. In: F Nielloud, G Marti-Mestres (ed). Pharmaceutical emulsion suspension. New York, Marcel Dekker, 2000: 383-407.
2. JE Kipp, JCT Wong, MJ Doty and CL Rebbeck. Microprecipitation method for preparing submicron suspensions. US Patent 6,607,784 2003.
3. X Zhang, Q Xia and N Gu. Preparation of all-trans retinoic acid Nanosuspensions using a modified precipitation method. *Drug Dev Ind Pharm.*, 32, 2006, 857-63.
4. P Kocbek, S Baumgartner and J Kristl. Preparation and evaluation of Nanosuspensions for enhancing the dissolution of poorly soluble drug. *Int J Pharm.*, 312, 2006, 179-86.
5. J Möschwitzer, G Achleitner, H Pomper and RH Müller. Development of an intravenously injectable chemically stable aqueous omeprazole formulation using Nanosuspensions technology. *Eur J Pharm Biopharm.*, 58, 2004, 615-9.
6. VB Patravale, AA Date and RM Kulkarni. Nanosuspensions: a promising drug delivery strategy. *J Pharm Pharmacol.*, 56, 2004, 827-40.
7. GG Liversidge, KC Cundy, JF Bishop and DA Czekai. Surface modified drug nanoparticles. US Patent 5, 145, 684, 199.
8. K Itoh, A Pongpeerapat, Y Tozuka, T Oguchi and K Yamamoto. Nanoparticle formation of poorly water soluble drugs from ternary ground mixtures with PVP and SDS. *Chem Pharm Bull.*, 51, 2003, 171-4.
9. A Wongmekiat, Y Tozuka, T Oguchi and K Yamamoto. Formation of fine drug particles by co-grinding with cyclodextrin. I. the use of  $\beta$ -cyclodextrin anhydrate and hydrate. *Pharm Res.*, 19, 2002, 1867-72.
10. HM Abdou, Dissolution. AR Gennaro, JB Schwartz. Eds. In: Remington's Pharm. Sci., Mack Publishing Company: Easton, PA, 18, 1990: 589-602.
11. DF Evans and H Wennerström. The Colloidal Domain: Where Physics, Chemistry, Biology and Technology Meet, 2nd ed.; VCH Publishers Inc.: New York, 1994.
12. MN Mosharra. The effect of particle size and shape on the surface specific dissolution rate of micro-sized practically insoluble drugs. *Int J Pharm.*, 122, 1995, 35-47.
13. RH Müller and C Jacobs. Production and characterization of a Budesonide Nanosuspensions for pulmonary administration. *Pharm Res.*, 19, 2002b, 189-194.
14. YC Liang and JGP Binner. Effect of triblock copolymer non-ionic surfactants on the rheology of 3 mol% yttria stabilised zirconia Nanosuspensions. *Ceram Int.*, 34, 2008, 293-297.
15. D Duchêne and G Ponchel. Bioadhesion of solid oral dosage forms, why and how. *Eur J Pharm Biopharm.*, 44, 1997, 15-23.
16. CJ Van Oss, DR Absolom and HW Neumann. Interaction of phagocytes with other blood cells and with pathogenic and nonpathogenic microbes. *Ann NY Acad Sci.*, 416, 1984, 332-350.
17. KH Wallis and RH Müller. Determination of the surface hydrophobicity of colloidal dispersions by mini-hydrophobic interaction chromatography. *Pharm Ind.*, 55, 1993, 1124-1128.
18. CM Keck and RH Müller. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. *Eur J Pharm Biopharm.*, 62, 2006, 62: 3-16.
19. F Kesisoglou, S Panmai and Y Wu., Nanosizing-Oral formulation development and biopharmaceutical evaluation. *Adv Drug Deliv Rev.*, 59, 2007, 631-44.
20. SP Vyas, YK Katare, V Mishra and V Sihorkar. Ligand directed macrophage targeting of amphotericin B loaded liposomes. *Int J Pharm.*, 210, 2000, 1-14.
21. RA Schwendener and H Schott. Lipophilic 1-beta-D-arabinofuranosyl cytosine derivatives in liposomal formulations for oral and parenteral antileukemic therapy in the murine L1210 leukemia model. *J Cancer Res Clin Oncol.*, 122, 1996, 723-726.
22. PU Xiaohui, Jin Sun, Mo Li and Zhonggui He. Formulation of Nanosuspensions as a New Approach for the Delivery of Poorly Soluble Drugs. *Curr Nanosci.*, 5, 2009, 417-427.