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A Systematic Review on Nanosuspension and its advancements

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Abstract

The solubility is the preferential criteria for the medicament to show pharmacological action. A pharmaceutical suspension is a coarse dispersion of insoluble solid particle in a liquid medium. One of the best suitable dosage forms for people who cannot take solid dosage forms. It contain solvents, buffering agent, preservative, antioxidants, wetting agent, anti-foaming agent, suspending agent and flavouring agent. Suspension dosage form incorporate effective distribution of lipophilic drug; mask a bitter taste, avoid the use of cosolvents and provide resistance to deterioration of drug due to hydrolysis, oxidation or microbial activity. In addition, nanosuspension is the novel and recent advancement in enhancing aqueous solubility of weakly soluble drugs. It not only increases aqueous solubility but increases bioavailability as well.

As a result of the significant improvement in bioavailability, the flexibility for surface modification and mucoadhesion for drug targeting have significantly expanded the scope of this novel formulation technology. Suspension allows for the absorption drug relatively higher than any other solution dosage forms. Different method of preparation are used with a solvent, suspending agent (HPMC and Methyl Cellulose) and Surfactant (Tween-80, and SLS). Introduction, preparation techniques, characterisation, and applications of the nano suspension are covered in this review article.

Key Words: Nanosuspension, Bioavailability, Suspending agent, Surfactants

Introduction

Nanosuspension is the submicron colloidal dispersion of nanosized drug particles.A pharmaceutical nanosuspension is defined as colloid, biphasic, dispersed, and solid particles with a size below 1 µm, in an aqueous medium, stabilised by surfactants and polymers and without of any matrix material. [1]The solid particles in nanosuspension generally have particle size a micron or smaller and particle size ranging from 200-600nm. [2] Nanosuspension not only increases solubility and bioavailability of drug but also modifies the pharmacokinetics of drug that improve the drug efficacy and safety. Nanosuspensions are used in drug formulation rather than lipidic systems for drugs that are insoluble in both water and organic media. The formulation method using nanosuspension is suitable for substances with high log P values, high melting points, and high doses.[3]The Nernst-Brunner, Levich modification and Noyes-Whitney equation states that decreasing drug particle size increases surface area, which in turn increases the rate of dissolution. The use of nanosuspension technology helps the drug to be kept in the necessary crystalline state with smaller particles, increasing its rate of dissolution and, subsequently, its bioavailability.

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The pharmaceutically acceptable states of the drugs included inside nanosuspensions are either crystalline or amorphous. Brick dust molecules can be successfully formulated as nanosuspensions for enhanced solubility and good absorption. [4]

Advantages

- Nanosuspension Increase the solubility and bioavailability of drugs.
- By formulating nanosuspension, higher drug loading may be obtained.
- Reduction of dose may possible.
- This dosage form enhances the physical and chemical stability of drug.
- Helps to provide a passive drug targeting.
- Can avoid and reduce tissue irritation.
- Can achieve long term physical stability.
- Nanosuspension is suitable for various routes administration.
- Oral administration of nanosuspension provide fast onset of action and increase bioavailability [5][6].

Table 1: Advantages of Nanosuspension over conventional formulation [5][6]

Route of administration	Disadvantages of conventional formulation	Advantages of nanosuspension
Oral	Slow onset of action/ poor absorption.	Rapid onset of action/ solubility and bioavailability can improve.
Intravenous	Poor Dissolution / nonspecific action	Rapid dissolution / tissue targeting
Ocular	Lachrymal wash off/low bioavailability	Higher bioavailability/dose consistency
Intra muscular	Patient compliance low due to pain	Tissue irritation reduced

Formulation of Nanosuspension

Table 2: Category wise list of excipients during formulation of nanosuspension [7][8][9]

Excipient	Function	Example
Stabilizer	Prevent Ostwald's ripening, agglomeration of the nanosuspension, and enhance self-life.	Lecithins, Poloxamer, Polysorbate, Cellulose Povidone, and its derivatives.[7]
Co- surfactant	Enhance the solid particles wettability and influence phase behaviour when micro emulsion are used to formulate nanosuspension.	Dipotassium,Glycyrrhizinate, Bile salts, Transcutol, Ethanol, Glycofurol and Isopropanol[7][8]
Organic Solvent	Used to dissolve hydrophobic drug compound excipients.	Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Propylene carbonate, Benzyl alcohol.[8]
Other additives	Used to increase formulation compliance and suitable for formulation	Buffer, Salts, Osmogenes, Polyols(sugar), and Cryoprotectant (protect the cells) , etc. [9]

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Method of Preparation of Nanosuspension

There are many ways to formulate a stable nanosuspension. The three types of nanosuspension preparation procedure are as follows.

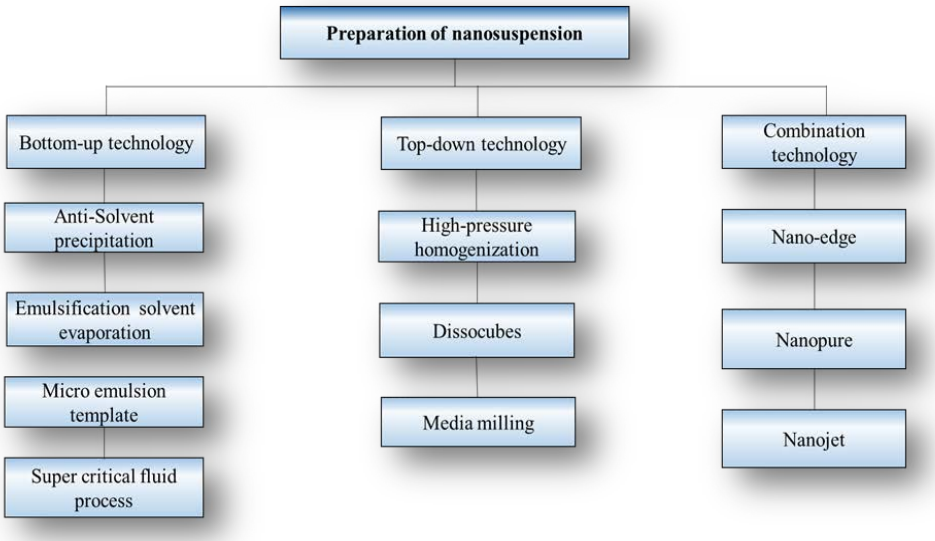

Fig. 1: Schematic diagram of method of preparation of nanosuspension [10]

Bottom up techniques

Solvent Anti-solvent method: Precipitation method is used for the preparation of the sub-micron particle. It is mainly used for poorly water soluble drug.In a suitable solvent, the drug is dissolved. In the presence of surfactants, this solution is subsequently mixed with a miscible anti-solvent system [11][16]. Rapid addition of the drug solution to the anti-solvent causes the drug to rapidly get supersaturated in the combined solution, resulting in the formation of ultrafine drug solids. Precipitation method involves two phase nuclei formation and crystal growth. In these technique drug is soluble in one solvent. [16]

Emulsification solvent evaporation technique: The process of emulsification solvent evaporation method the polymer is prepared are volatile solvent and emulsion. After the solvent for the polymer evaporates, the emulsion turns into a suspension of nanoparticles that is then allowed to permeate into the continuous phase of the emulsion. The particle size affects the concentration of polymer, stabilizer and speed of homogenizer. [15]

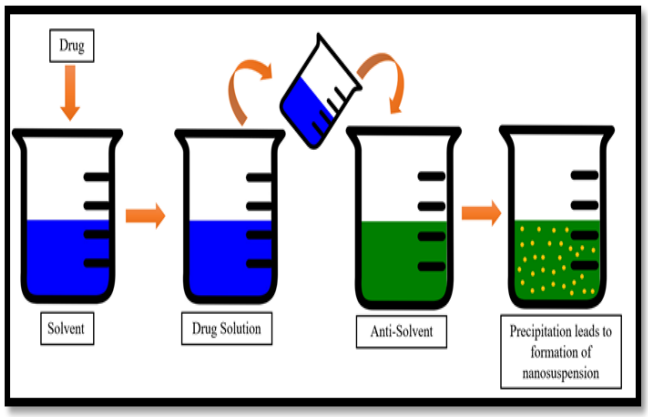

Fig. 2: Systematic representation of solvent anti-solvent precipitation method [29]

Lipid emulsion/ micro emulsion templete: another method to produce nanosuspension is to apply the emulsion formed by the conventional technique using partially water miscible solvent as dispersed phase. Nanosuspension can be received by just diluting the emulsion and through micro emulsion as template. [13] An interfacial coating of surfactant and co-surfactant stabilises micro emulsions, are the thermodynamically stable mixtures and isotopically two transparentimmiscible liquids are dispersed, such as water and oil. The drug can be thoroughly

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mixed into the pre-formed micro emulsion or it can be loaded into the internal phase.However, the use of organic solvents has an impact on the environment, requiring the use of significant quantities of stabiliser or surfactant [11][16].

Super critical fluid technology: Super critical fluid technology can be used to formulate nanoparticles from drug solution. Three different approaches have been attempted Precipitation with compressed anti-solvent process (PCA), Supercritical anti-solvent process, and Rapid expansion of supercritical solution (RESS).The RESS involves expanding the supercritical fluid drug solution through a nozzle, which causes the supercritical fluid to lose solvent power and cause the drug to precipitate as micro particles [14][16]. This method was used by Young et al. to create cyclosporine nanoparticles between 400 and 700 nm in size. The PCA technique involves atomizing the drug solution into a container containing compressed CO_2. The solution becomes supersaturated as the solvent is withdrawn, which causes it to precipitate as small crystals. A drug that is poorly soluble in a supercritical fluid is used in the supercritical anti-solvent procedure with a drug solvent that is also miscible with the supercritical fluid [15].

Top down techniques

High pressure homogenizer: It is the most popular method for producing nanosuspensions of many drugs with low aqueous solubility. The presuspension is homogenised at low pressure in a high pressure homogenizer for premilling. To make nanosuspensions of the desired size, presuspension is finally homogenised at high pressure for 10 to 25 cycles. On the basis of this theory, various techniques have been developed for making nanosuspensions, including:[17]

- Homogenization in aqueous media (Disso cube)
- Homogenization in non-aqueous media (Nanopure)
- Combined precipitation and homogenization (Nano edge)
- Nano jet

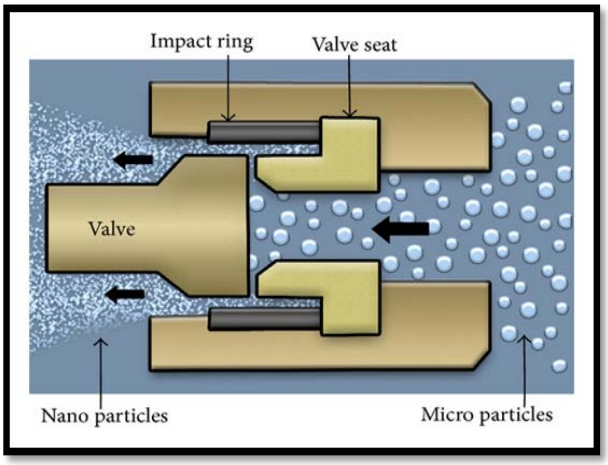

Fig. 3: Systematic representation of high-pressure homogenization [30]

Homogenization in aqueous media (Disso cube): Using a high-pressure homogenizer of the piston-gap type, R. H. Muller developed this technique in 1999[17]. This process involves forcing the drug and surfactant suspension under pressure using a high-pressure homogenizer that has a nanosized aperture valve. The aqueous phase cavitation is the basis of this method. [12] The cavitation forces of the particles are strong enough to transform the drugs micro particles into nanoparticles. Problems arises due to the requirement for small sample particles prior to loading and the several cycles of homogenization required [14].

Non-aqueous media homogenization (Nanopure): The non-aqueous drug suspensions medium have been homogenised at 0 °C or even below the freezing point and are known as "deep-freeze" homogenization.[12][13] Nanopure is suspensions homogenised in water-free media or water combinations.The outcomes were similar to Disso Cubes method, so they can be employed effectively for thermolabile compounds under more tolerant circumstances. Drug nanocrystals suspended in liquid polyethylene glycol (PEG) or a number of oils can be placed directly into HPMC capsules or gelatin as drug suspensions [14].

Combined precipitation and homogenization (Nano edge): An organic solvent is used to dissolve the drug, and the resulting solution is mixed with a miscible anti-solvent to precipitate it.The drug precipitates because of the low solubility in the water-solvent mixture. High shear processing has also been combined with precipitation [17]. This is done through high-

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pressure homogenization and rapid precipitation. The blended solution unexpectedly becomes supersaturated and generates fine crystalline or amorphous particles when a drug solution is added quickly to an anti-solvent. It is also possible to appreciate the precipitation of an amorphous substance at high supersaturation when the solubility of the amorphous state is exceeded [18]

Nano-Jet: It utilizes a chamber where a stream of suspension is divided into two or more sections that colloid with one another under high pressure as a result of the high shear forces produced during the process, which reduces particle size. This technique is also known as opposite stream technology.The main drawback of this method is the high number of passes (approximately 75) needed through the micro fluidizer, and the amount of micro particles in the final product. This technique' drawback is that it demands long production times [14].

Media milling: The method was first developed by Liversidge *et al*. in 1992. The nanosuspensions are introduced in high shear mills. The milling chamber is rotated at very high shear rate for at least 2 to 7 days at fixed temperature. Milling media containing water, drug and stabilizing agent. The milling media is made up of zirconium oxide, or a polystyrene resin with a high degree of bonding. [19]The high energy and shear forces generated as a result of the impaction of milling media with the drug provide the energy input the microparticle drug into nanosized.[20]

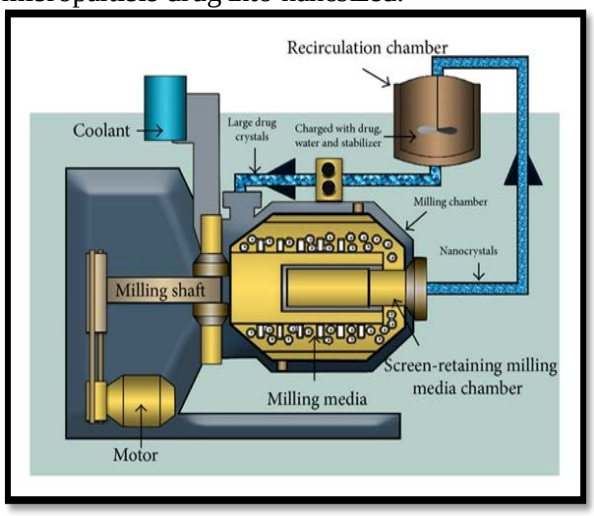

Fig. 4: Systematic representation of the media milling process [30]

Characterization of nanosuspension

Colour, Odour, Taste evaluation: These characteristics have particular importance in formulations designed for oral administration.A change in crystal behaviour and particle size that affects dissolving. The indication of chemical instability can be colour change, smell or taste. [21].

Particle size distribution: Particle size distribution should indicate the physiochemical characteristics of the formulation, such as saturation solubility, ability to dissolve, and physical stability. Laser diffraction (LD), photon correlation spectroscopy (PCS), coulter counter multi-sizer are used to particle size determination [21].

Zeta potential: the determination of zeta potential of the formulated nanosuspension is essential as it gives an idea about physical stability of the nanosuspension. it is governed by both the drug and the stabilizer itself. For the electrostatically stabilized nanosuspension, a minimum zeta potential of 30mV is required whereas in the case of combined electrostatic and steric stabilization a minimum zeta potential of 20mV is desirable. [21][22]

Crystalline state and particle morphology: The crystalline state and particle morphology help in identifying the morphological or polymorphism modifications that a drug may undergo as a result of nanosizing. The high pressure homogenization nanosuspension change in the crystalline structure which is amorphous form to another polymorphic form which is determined by X-ray diffraction, DSC. Scanning electron microscopy is preferred to get the actual morphology of the particle. [22]

Saturation solubility and dissolution tendency: Since enhanced saturation solubility can also speed up dissolution, nanosuspensions have a great benefit over other approaches.These two parameters need to be measured in various physiological solutions. The study of saturation solubility and dissolving velocity is essential for determining how well a formulation performs *In vitro*. The dissolve pressure and velocity of nanosuspension have increased, which can be linked to the nanometre ranging particle size [22].

Droplet size: The droplet size can be determined by electron microscopy and light scattering technique. Light scattering used as a neon laser wavelength in 632nm [21].

Viscosity measurement: The viscosity of the nanosuspension at different shear rates at different temperature can be measured using Brookfield viscometer. The room temperature must be 37°C by thermo bath and the sample, are to be immersed in it [21].

Drug content: In order to separate the drug from the nanosuspension formulation, use a solvent mixture such as Methanol: THF (1:1), shake well, and centrifuge. The absorbance is measured at a suitable λ max after the supernatants are separated and diluted with the same solvent mixture. The calibration curve is used to calculate the drug content [23].

pH value: pH can have an impact the stability of a nanosuspension, so it's important to determine the pH before formulating any drug that will be administered topically, orally, and intravenously. It can be determined by digital pH meter[24]

Pharmaceutical Application of Nanosuspension

Oral drug delivery: The primary issue with oral drug administration is poor solubility, incomplete dissolution, and insufficient effectiveness. Due to a higher surface area and smaller particle size, oral nanosuspensions are specifically utilised to boost the bioavailability and absorption rate of low water soluble drugs.Benefits of the nanosuspension include enhanced oral absorption, dosage proportionality, and minimal intersubjective variability. Drug nanosuspensions can be easily administered by different dosage forms, which includes tablets, capsules, and rapid melts, by using normal manufacturing procedures [25][17].

Parenteral drug delivery: Micellar solutions, salt production, solubilization employing cosolvents, the complexing of cyclodextrin, and more recently vesicular systems like liposomes and niosomes are among the modern techniques for parental administration.However, these approaches have drawbacks, including low solubilization potential, low parental acceptability, high manufacturing costs, etc. The technology of nanosuspension is used to solve the above issues.Numerous parental routes, including intraarticular, intraperitoneal, intravenous, are used to give nanosuspensions. Additionally, nanosuspensions improve the effectiveness of drugs taken through parenteral route [25][26].

Ocular drug delivery: Ocular drug delivery for the Nanosuspension is used for sustained release. Using Eudragit, Liang and colleagues created cloricromene nanosuspension for ocular administration. An experiment showed that the rabbit eye's aqueous humour has a higher drug availability. As a result, nanosuspension formulation presents a possible means of enhancing the drug's bioavailability and shelf life following ophthalmic application [27][17].

Pulmonary drug delivery: In pulmonary drug delivery nanosuspension are nebulized through mechanical or ultrasonic nebulizer.All aerosol droplets contain drug nanoparticles because they contain a lot of microscopic particles. For pulmonary administration, budesonide corticosteroid has been effectively produced as a nanosuspension. Because of the small particle size, aqueous solutions of the drug are easily nebulized and administered via the pulmonary route. For the administration of liquid formulations, various nebulizer types are available [27][15].

Targeted drug delivery: The surface characteristics of nanosuspensions make them suited for targeting certain organs. Furthermore, by changing the stabiliser, *In vivo* behaviour can be easily modified.This can be used to direct antifungal, antimycobacterial, or antileishmanial medications towards macrophages if the infections remain active inside cells. [27,15].

Marketed drugs in form of nanosuspension in different route of administration [28][14]

Route	Drugs	Therapeutic class	Brand name	Company
Oral	Azithromycin	Antimicrobial	Zithromax	Pfizer
	Griseofulvin	Anti-fungal	Gris-PEG	Glaxo-smithkline pharmaceutical
Parental	Naproxen	Anti- inflammatory	Naprosyn	Adva care pharma
Intravenous	Acyclovir	Antivirotic	Zovirax	Glaxo-smithkline

				pharmaceutical
Ophthalmic	Hydrocortisone	Glucocorticoid	Cortef,Cortifoam	Pfizer
Pulmonary	Budesonide	Asthma	Pulmicort , Duoresp	Cipla Ltd
Intrathecal	Busulfan	Anti-cancer	Myleran , Busilvex	Amneal Pharmaceuticals, Inc.
Topical	Silver sulfadiazene	Eczema	Silvadene	SHC Pharmaceutical

Conclusion

One of the major problem with poorly soluble drug has very low bioavailability. Nanosuspension technology is able to enough to bring enormous immediate benefit. Prepration of nanosuspension not only solve the problems for poor solubility and bioavailability but also improve drug safety and efficacy. Nanosuspension appears to be a novel and yet cost effective strategy. Drugs with lipophilic nature and that are poorly soluble in aqueous and organic solution have a low bioavailability problem that can be successfully solved using a combination of the methods described in this study either alone or in a combination. Since nano- technique is simple, require less excipients and increases the dissolution velocity and saturation solubility, it will continue to be the application various routes of administration.

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