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Review on Application of Nanosuspension An Approach to Improve the Poor Solubility of Drug

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Abstract
When we develop a new formulation one of the critical factors is solubility, nanosuspension is a very great approach to improve the poor solubility of drug as well as great technique for improvement in bioavailability. Nanosuspension is easy to prepare and more beneficial as compare to other conventional dosage form. Oral preparation and non-oral preparation for both nanosuspension can be used. When the size of drug particle is reduced in a sub-micron size dissolution rate is increase which result the enhancement of bioavailability. Nanosuspension not only improve poor solubility problem also improve pharmacokinetic profile. These review article include different nanosuspension technologies, their characterization, property and pharmaceutical application of nanosuspension.

Keywords
Nanosupension, Technology and Manufacturing process.

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INTRODUCTION[1-11]
The improvement drug which are poorly soluble in water is also a challenging problem for scientist. Nanosuspensions is the type of suspension in which drug particle are submicron colloidally dispersed in nanosized in nanosuspension stability is usually achieved by the use of surfactant. Nanosuspension are colloidal in nature and generally stabilized by addition of polymer and surfactant.

Nanosuspension may be define as that nanosuspension is a biphasic system which is consist of drug particle which is pure and dispersed in aqueous vehicle in which the suspended particle diameter is generally less than 1µm in size. Now days various method used for the treatment of drug that are poorly soluble which include micronization, solubilization using co-solvents, salt form, surfactant dispersions, technique like precipitation, and oily solution.

Other techniques involve liposomes technique, emulsions technique, microemulsion technique, solid dispersion technique and inclusion complexation which is usually used cyclodextrins. The technique is always use for drug which has no solubility in water and organic solvent. Which result solubility is higher, and also the flooding rate of the active pharmaceutical ingredient is increase and reaches at maximum plasma level faster.

Nanosuspension are uses for both poor soluble drug as well as poor permeable drug. They reduce particle size significantly, so it is also useful for intravenous administration in order to prevent the blockade of blood capillary.it has the advantages of liquid formulations over others. Atorvastatin, famotidine, simvastatin, revaprazan, aceclofenac all are hydrophobic drug and formulated all above drug as nanosuspension.

ADVANTAGES [12-13]:-
1. It can apply only for poorly soluble drug. Batter biological performance can be achieved due to

higher rate of dissolution, saturation solubility of drug.
2. Reduced tissue irritation.
3. Higher physical stability in presence of stabilizer.
4. Higher bioavailability for ocular administration as wll as inhalation drug delivery.
5. Nanosuspension can be transformed into cream, gel, pellet, capsule and tablet.

DISADVANTAGES: -

1. The one of the difficult problems with nanosuspension is the problem of sedimentation as well as compaction and physical stability.
2. Special treatment is required during transport and handling because it is bulky.
3. Dose uniformity are not achieved otherwise suspension are in a proper dose.

DIFFERENT TECHNOLOGY FOR PREPARATION OF NANOSUSPENSIONS [14]

Technically nanosuspension preparation are simpler as compare to liposomes preparation and also other type of conventional drug carrier. But it is less economic because it is costly. It is many for the drugs that are poorly soluble. In order to prepare nanosuspension mainly to converse method are used namely "top - technology". The top-down process follows the disintegration approach from larger particles, microparticles to nanosized particles.

1. Media milling technique [15-16]: - These is first proposed by Liversidge (1992). In these technology by high sher media mill nanosuspension are prepared ed. In these method with the milling media, water, drug and stabilizer, was charged for at least 2-7 days. The milling media is usually consisting of glass, zirconium oxide or highly cross-linked polystyrene resin. In these technology the high energy shear forces are formed which result milling media impaction which result the particle size reduced.

2. High pressure homogenization [17-19]: - High pressure homogenization method is usually used for poor soluble drugs. In this method forcing a suspension which contain drug and stabilizer through a suitable valve with small orifice under pressure. or in these methods the suspension is forced under high pressure through a valve which having a narrow aperture. Disco cube was the invention of muller. In muller method the suspension is passed by small orifice which result significant reduction in static pressure follow the water boiling pressure, which result the boiling pressure is increase and gas bubbles are form. The bubble implied if suspension leave the gap and normal air pressure can be reached again in these methods the drug particle are contain in surrounding part which pushes into the center which result significant reduction in the particle size. The great advantage of this process is that it can be utilize for both dilute and concentrated suspension. The high-pressure homogenization process is much more batter then the media milling.

3. Microprecipitation - high pressure homogenization technique [21-22]: -

Nano edge technology these technologies is the invention of muller *et al*. 75 these consist of 2 process by high pressure homogenization drug particle can be precipitated and their fragmentation in these technique to different solution are added. These 2 solution are water miscible and form organic phase .in these technique in aqueous phase stabilizer are dissolve in which the active pharmaceutical ingredient is usually insoluble mixing of these 2 solution causes problem of drug particle precipitation the final stage of these process is called high pressure homogenization . The example of nano edge technology is the itraconazole nanosuspension.

4. Nanoedge [23]: - These are the combination technology. These technologies include precipitation and homogenization combination. The basic principal is similar to that of precipitation and homogenization. These methods usually friable material precipitated which is followed by fragmentation under high shear and/or thermal energy. The main advantage of these technique is that smaller the particle size and batter stability, but the disadvantage of precipitation is that it is not beneficial technique for long-term stability. And crystal growth is also the drawback of precipitation technology. But the crystal growth and stability problem can be improved nanoedge technology in these techniques usually water miscible solvent is use water like Methanol, ethanol and isopropanol.

5. Nanojet technology [24]: - These is also called opposite sream technology.

In these technologies usually chamber is uses in these suspension stream has two parts or more than two parts which will be colloid with each other at high pressure, in these technique particle sizes is reduced because of high shear forces. The main disadvantage of these technique through the microfludization high number of passes and the resulting product relatively larger microparticle fraction emulsion.

6. Diffusion method [25-27]: - In these methods, usually partially water miscible and volatile organic solvent are used. For example, n-butyl lactate, benzene methanol, glyceryl triacetate, ethyl ester, and ethyl acetate as the dispersed phase. The emulsion is prepared by dispersing the drug loaded in a mixture of different solvent. In these method

dilutions is responsible for the formation of nanosuspension in these internal phased is diffused into the external phase when droplet convert into the particle. The size of particle is determined by emulsion droplet size. The major drawback of these technology is in the last products presence of residual solvent because of potential environmental hazardous and Huma safety issue. The acyclovir nanosuspension is manufactured by emulsion diffusion method.

7. Melt emulsification method [28]: - The first nanosuspension which is prepared by melt emulsification method is ibuprofen the kipp *et al*. Firstly, utilized these techniques in order to prepare nanosuspension of ibuprofen. These processes consist of four steps. Firstly, the drug is added to the aqueous solution in aqueous solution the stabilizer is contain. Then the solution is heated at temperature more than the melting point of the drug and then it homogenized with the help of high-speed homogenizer in order to obtained nanosuspension. The maintenance of temperature is very essential in this technique. And the temperature should always more than the drug melting point. The nanosuspension particle size depend upon concentration of drug, type of stabilizer, cooling temperature and homogenization process.

8. Supercritical fluid method [29]: -

To produce nanoparticle various method are used these methods include rests, super critical antisolvent process in combination of compressed antisolvent process. In RESS method drug solution is expanded into supercritical fluid by a nozzle the result of these as fine particle drug is precipitately of the super critical fluid solvent power are loss. On other hand in the PCA method the drug solution into the carbon dioxide chamber is atomized the solution get supersaturated as solvent removal is occur which result precipitation occur. On the other hand, in supercritical antisolvent process, the drug in the form of solution is introduced into the supercritical fluid and solvent get extracted and then the drug solution become drug saturated.

9. Dry co-grinding [30-31]: - These is the recent advancement in the field of emulsion technology these techniques describe that nanosuspension can also be obtained by dry milling technology. In these techniques different of polymer and co-polymer are used the polymer and co-polymer examples are polyethylene glycol (peg), HPMC and cyclodextrin derivative.

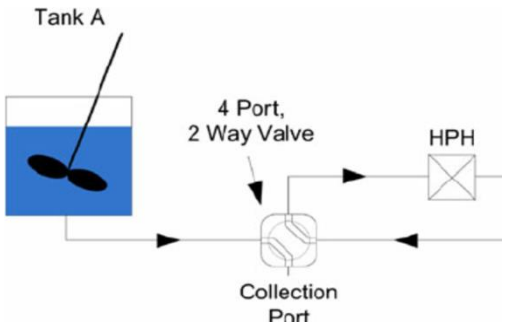

Fig. No. 1 For preparation of nanosuspension high pressure homogenization apparatus.

Table 1: - Name of different homogenization technique, company name, and patent number. Processes [20]

Technology	Company	Patent number
Dissocubes	Sky pharma	Us 5,858,410
Nanopure	Pharma sol	Pct/ep00/0635
Nanocrystal™	Élan nano systems	Us 5,145,684
Nanomorph™	Soligs/abbott	D 1963 7517

FORMULATION CONSIDERATION

1. Stabilizer
2. Organic solvent
3. Co-surfactant
4. Other additives

1. Stabilizer [32-33]: - stabilizer play major role in the preparation of nanosuspension.

The key role of stabilizer is to wet the drug particle, and to prevent Ostwald ripening ad agglomeration these stabilities of nanosuspension. The pharmaceutically acceptable stabilizer are poloxamers, polysorbate, cellulosic, povidones and lecithin. Lecithin is ideal stabilizer for parenteral nanosuspension.

2. Organic solvent [32-34]: - if emulsion and micro emulsion is used as template.

These solvents are very hazardous the organic solvent is used methanol ethanol, chloroform, isopropanol and partially water miscible solvent such

as ethyl thanoate, formic acid, butyl lactate, benzyl alcohol because its less hazardous then the conventional dichloromethane

3. Surfactant [35]: - Surfactant is used to improve the dispersion by significant reduction in interfacial tension. They act as wetting or foaming agent. example - tween-80 or span.

4. Co-surfactant [32]:- the effect of co-surfactant on uptake of the internal phase for selected micro emulsion composition and on drug loading should be investigated, although the literature describe that the bile salt and co-surfactant such as dipotassium, nglycerrhizinate, transcutol, glycofurol, ethanol and isopropanol as a solubilizer can be used in the formulation of microemulsion.

5. Other additives [32]: - the other additives that involve in nanosuspension are salts, buffer, osmogent, cryoprotectant.

PROPERTIES OF NANOSUSPENSION: -

1. Temperature [36]: - During the preparation of nanosuspension the maintainace of optimum temperature is essential. In the homogenization process the formulation should be prepare at low temperature.

2. Physical long-term stability [37]: - For crystal growth usually Ostwald ripening is responsible and the main problem which is associated with dispersed system is physical instability. The reason of Ostwald ripening is the change in the dissolution velocity as well as saturation solubility of particle that are small in size and the particle that are large in size.

INTERNAL STRUCTURE OF NANOSUSPENSIONS [38-43]

During the process of disintegration, the higher energy input is responsible for structural change within the drug particle. When the particle of drug is exposed to pH. the particle is converting into amorphous state from the state of crystalline, drug hardness, homogenization cycles, drug chemical nature, power density which is applied by homogenizer is responsible for change in state.

POSTPRODUCTION PROCESSING [44-45]

Surface modification technique: - If nanosuspension are rapid or burst release may cause various side effects. Hence at the site of action in order to control release and prolonged residence time the modification of surface is required. For instance, nanosuspensions used for targeting the monocyte phagocytic system (mps) in the treatment of lymphatic mediated diseases can cause toxicity due to accumulation of drug. Showed that by layer-by-layer nanogels coating of procaine hydrochloride decreases the burst release of drug.

CHARECTERISTION OF NANOSUSPENSION [46-48]

1. Particle size distribution
2. Zeta potential
3. Crystal morphology
4. Dissolution velocity and saturation solubility

1. Particle size distribution: - Particle size distribution determines the physicochemical behavior formulation these include saturation solubility, dissolution velocity, physical stability etc. the particle size can be significantly determined by photon correlation spectroscopy and the pcs method. The pcs method has a measuring range of 0.05-80 m. The lid method can be measure particle 3 nm to 3m3 in size range 22 much more batter then the lid. method because it gave particle of absolute number for iv administration particle should be use les then 5 meu m. Because higher particle can cause blockade in capillary and embolism. 28 by pcs we can also identify the width of particle size distribution (polydispersity index, pi). 0.1-0.25 value of pi indicates fairly distribution of narrow size. If it is greater than the 0.5 indicate distribution is very broad. The coulter counter method is much more batter then the ld method it gives absolute no of particles per volume unit for the different size classes.

2. Zeta potential: - indication nanosuspension stability scanning calorimeter and differential thermal analysis can be used. High pressure homogenization is responsible for change in crystalline structure, which may be amorphous or other polymorphic form.

3. Crystal morphology: - To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, X-ray diffraction analysis, differential scanning calorimetry. Nanosuspension can cause modification in the crystalline structure because of high pressure homogenization which may be amorphous or other polymorphic form.

4. Dissolution velocity and saturation solubility: - Dissolution velocity and saturation solubility determined in various physiological solutions. Dissolution of drug is directly proportional to the drug particle surface area from micrometer to nanometer. These two parameters help in determining formulations in vitro behavior and also *in vivo* behavior (blood profiles, plasma peaks, and bioavailability) of the drug. Bohm *et al*. reported an in-dissolution pressure as well as dissolution velocity with a reduction in the particle size to nanometer range. The particle size is responsible for dissolution pressure. Muller explained that the energy introduced during the particle size reduction process

is directly proportional to the surface tension and as well as increase in dissolution process.

PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

1. **Oral drug delivery** [49] **:-** one of the major problem of nanosuspension is poor solubility and dissolution are incomplete and insufficient efficacy. The main application of nanosuspension increase the rate of absorption as well as bioavailability drug, because of smaller particle size and higher surface to volume ratio. The advantages of nanosuspension are improvement in oral absorption, proportionality n dose, and low inter subject variability. The drug nanosuspension can be significantly incorporate into different dosage form like solid dosage form tablet, capsule and sterile dosage form such as parenteral nanosuspension of ketoprofen can be easily incorporated into pallet in order to produce sustained release of drug over the period of 24 hours.
2. **Parenteral drug delivery** [50-56]**: -** nanosuspension enhance the efficacy of parenterally administrated drugs. There are number of approaches are used for parenteral drug delivery solubilization, salt formation, vesicular system such as noisome and liposome but these all above methods have some limitation like solubilization capacity parenteral acceptability, high manufacturing cost, etc. Parenteral nanosuspension formulation of drug which are poorly soluble in water are emerged. The nanosuspension of antineoplastic agent are prepare successfully. Nanosuspension for an aesthetic agent, antifungal agent, and antibacterial agent, hypothalemia and cancer pain are also prepared. It can be administrated by various route. If iv administrated drug is not dissolved instantly it will be distributed to the mps organ to overcome the above problem nanosuspension technology is used. Paclitaxel nanosuspension of paclitaxel was showed to have their superiority in reduction of median tumor burden.
3. **Pulmonary drug delivery** [57-58]**: -** Through mechanical or ultrasonic nebulizer nanosuspension can be nebulized for pulmonary administration. All aerosol droplet contains drug nanoparticles because of presence of many small particle. For pulmonary drug delivery budesonide nanosuspension have been successfully prepared. Suspension of drug in aqueous form can be significantly nebulized and administrated by pulmonary route because of the size of particle is very small. Budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, leuprolide, doxorubicin, etc. All drug successfully tried ith pulmonary route.
4. **Ocular drug delivery** [59]**: -** nanosuspension is a very great approach for those drug that show poor solubility in eye fluid usually lachrymal fluid. The eye protective make difficult with no tissue damage. Poor drug absorption and drug penetration to the intraocular tissue limits the delivery of drug. Hence nanosuspension is the best approach for ocular drug delivery.
5. **Targeted drug delivery** [60]**: -** now days nanosuspension are successfully used for targeted drug delivery due to their surface property and in vivo behavior. Kumar biswajit used for targeting anti-mycobacterial, fungal or leishmanial drug to macrophage. Scholar *et al*. showed an improved drug targeting to brain in order to treat toxoplasma encephalitis in a new murine model infected with toxoplasma Gondi using a nanosuspension formulation of atovaquone.
6. **Mucoadhasion of nanoparticle** [61]**: -** Nanoparticle orally administrated in suspension form that diffuse into liquid media rapidly encounter the mucosal surface. The first step for mucoadhasion is with direct contact of drug particle to the intestinal cell before particle absorption. The adhesiveness of nanosuspension not only help in bioavailability improvement it also helps in targeting of parasite that persisting in the gastrointestinal track for example cryptosporidium parvum. Due to the residence time longer at the site where infection. Nanosuspension of buparvaquone are used the bioadhasion can also improve.

CONCLUSION

The main aim of these review to describe various type of nanosuspension technology. If nanosuspension is prepare in large scale the most suitable techniques are media milling and high-pressure homogenization technology. The problem of poor aqueous solubility of drug can be improve by use of nanotechnology and nanosuspension is the integral part of nanotechnology. By reducing size in a submicron range the solubility of drug can be enhanced and also bioavailability of drug. Nanosuspension is can be administrated through various route the route includes parenteral route, ocular route, pulmonary route, oral route etc.

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