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Nanosuspensions as a promising approach to enhance bioavailability of poorly soluble drugs : An update

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ABSTRACT

Solubility is a vital factor for devloping drug delivery systems for poorly water soluble drugs. Several conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly water soluble. Nanosuspension technology can be used to enhance the solubilty, stability as well as the bioavailability of poorly water soluble drugs. Nanosuspensions are biphasic systems comperising of pure drug particles dispersed in an aqueous vehicle, stabilized by surfac active agents. Fabrication of nanosuspension is simple and more advantageous than other approaches. Techniques like high-pressure homogenization, wet milling, emulsification, solvent evaporation, bottom up technology and top down technology have been applicable in the fabrication of nanosuspensions. Nanosuspension delivery is possible by several routes, such as oral, pulmonary, parenteral and ocular routes. Nanosuspension not only solves solubility and bioavailability issue, but improve drug safety and efficacy. In this context, we reviewed the current techniques used to develop nanosuspensions and their recents studies application in drug delivery system.

Keywords : Solubility, fabrication, Characterization, Applications, Nanosuspension.

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INTRODUCTION

In recent years, more than 40% of the new chemical moities being generated by drug discovery projets are lipophilic in nature or poorly soluble in water. Developing poorly water soluble drug has always been a challenging issue confronted by the pharmaceutical researchers. To tackle this issue, nano sized formulation of these compunds can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and attaining higher bioavability. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility [1,2].

Nanosuspension is a colloidal formulation of very small particles (nanosized) of drug in which stabilized by surface active agents. The termNanosuspension was derived from two words nano and suspension. Nano is related to very small (nano range) and suspension is biphasic dosage form which is the combination of two phases, namely dispersed phase and another one is dispersion medium. Generally, nanosuspensions are mainly used to increase physicochemical properties as well as safety and efficacy of drugs which have low solubility[3].

ADVANTAGES AND DISADVANTAGES OF NANOSUSPENSIONS[4]

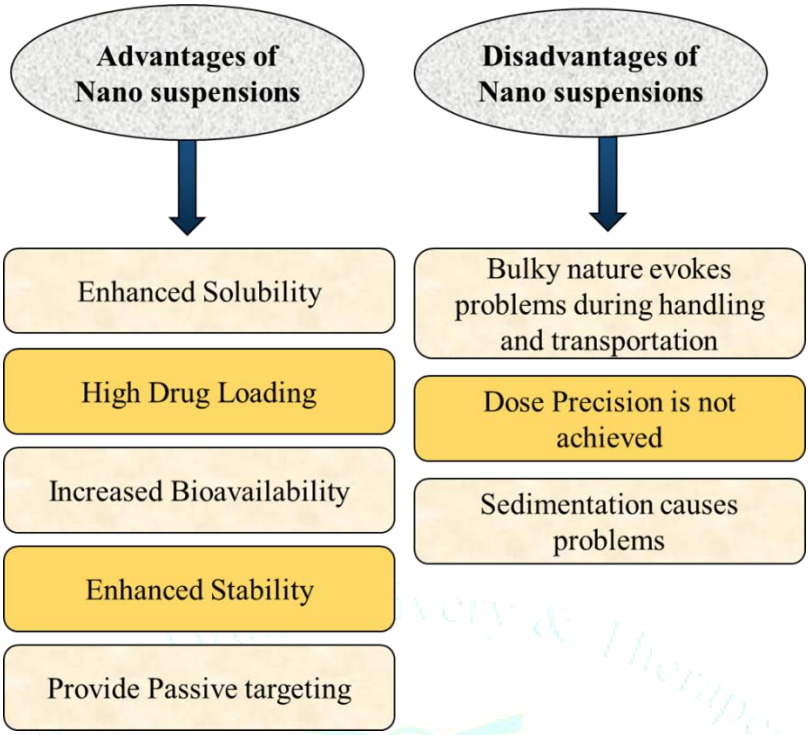

Figure 1: Advantages and Disadvantages of Nanosuspensions

FABRICATION TECHNIQUES OF NANOSUSPENSIONS

In current scenario, Bottom-up technology and Top-down technology are two approaches are used for preparation of nanosuspensions. Normally, micronisation technique is most probably used for preparation of nanosuspensions and it is carried out by jet or media milling. (Muller and Peters et al, 1995).This method has few limitations such as it enhances only dissolution profile of drug but lacks saturation solubility. Thus, researchers are finding some alternative techniques to preapare nanosuspensions. Further some techniques are described with their advantages and disadvantages [5,6,7].

1. Bottom upTechnology

As the name suggests, this approach starts from the bottom i.e start from molecular level and lastly goes to molecular association for the formulation of small solid particles. This means it is novel precipitation technique in which the solvent quantity should be reduced [8].

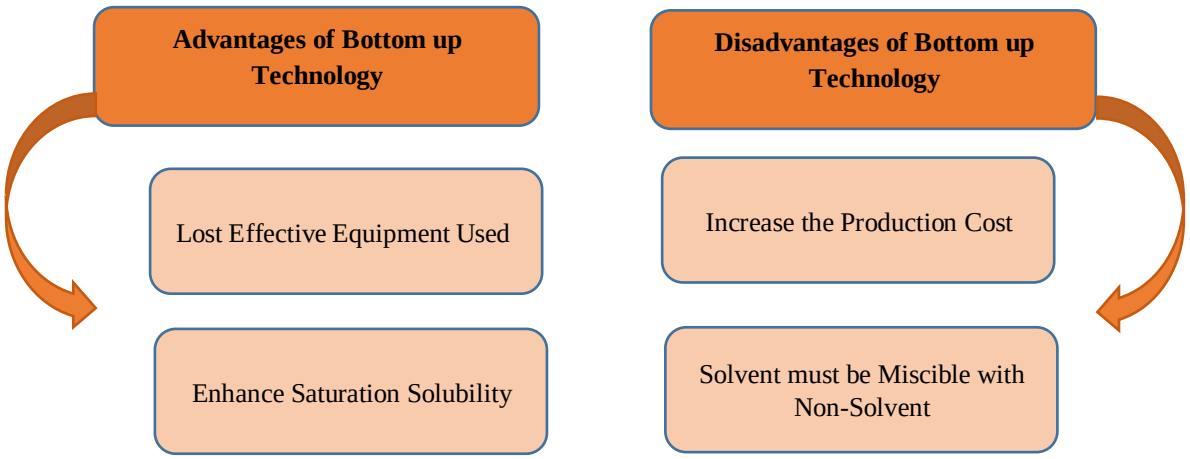

Figure 2: Advantages and Disadvantages of Bottom up Technology

2. Top down Technology

Top down approaches involves techniques like Grinding (media milling), High pressure homogenization, Nanopure, Combined precipitation and homoginisation (nanoedge), Nanojet Technology, Emulsification-Solvent Evaporation techniques, Hydrosol method, Supercritical Fluid Method, Precipitation technique, Dry-co-grinding[9].

2.1 Grinding Technique (mediamilling)

In this technique, nanosuspension is formed by reducing the

particles size by the help of pearl and media mills. This milling equipment is mainly consists of shaft, milling cabinet, and recirculation cabinet. For example, the planetary ball mill can reduce the particle size up to 0.1µm. This approach is very simple, cost effective and can be possible to scale up. However, contamination can be occur during this technique, as using milling for longer duration increses germ growth in acquos phase.

2.3 High Pressure Homogenization

This approach is mainly used for those drugs which show low solubility.This strategy includes constraining an course suspension, which contains drug and stabilizers through a valve with a little hole under pressure [10].In this course, suspension is employed through a small area with high pressure up to 1500 bar and the result in enhance the dynamic pressure with concurrent decrease in the static pressure, which decreases the water's boiling point to normal (room) temperature. Thus, at the normal (room) temperature water will start boil and create gas bubbles. When suspension leaves the gap or area and the pressure returns to the atmospheric level, the gas globules crash. This process is called as cavitation. The combined forces of cavitation, high shear, and collisions lead to fracture of the drug microparticles into nanosized particles [11].Number of homogenization cycles, homogenization pressure, hardness of drugs, and temperature (when thermosensitive drugs are processed) are factors that influence the physical characteristics (such as particle size) of resulting nanosuspensions. Metal contamination because of the erosion is less pronounced in this technique than in media milling. This technique is also a safe technique for producing nanosuspensions. Less than 1 ppm metal contaminations were detected under processing condition of 20 cycles and pressure of 1500 bar [11,12]. The major drawback of this method is the need for pretreatment to obtain microparticles before starting the homogenization process and the more cycles of homogenization[13]. For various purposes such asdispersing drugnanocrystals in low molecular weight PEG or in oil, liquid nanosuspensions are dispersed in nonaqueous media or media with reduced water content. As the low vapour pressure and high boiling point of oily fatty acids and oils, the drop in pressure is not sufficient for cavitation, thus the latter is not a determining factor in this process. To compensate for insufficient drop in pressure, the nanopure processis directed at low temperature which is often referred to as -deep- freeze‖ method. Conducting the process at 0◦C or even less than 0◦C (freezing point) produces results comparable to those achieved using dissocubes [14].

Types of Pressure Homogenization

2.3.1 Homogenization in Non-Aqueous Media(Nanopure)

This is another type of preparation technique of nanosuspension which involves homogenization in water mixtures or water free media and is prepared for the thermolabile compound. Nanopure is also called as deep freezing because homonigenation of drug suspension is carried out in non aqeuous media at 0^0C temprature i.e. the drug suspensions in the non-aqueous media were homogenized at 0°C or even belowthe freezing point andhence are called -deep freezehomogenization [2].

2.3.2 Combined Precipitation & Homogenization (Nanoedge)

As the name indicate both precipitation and homogenization are carried out at same time. Combined precipitation is also called as nanoedge in which drug mixed in an organic solvent and then the solution is also mixed with a miscible anti-solvent for precipitation. Solubility is low in case of water-solvent mixture and drug precipitates. Precipitation has also been coupled with high shear processing. Principles of Nanoedge is the similar as precipitation and homogenization. This technique make particle size in nano range and give better stability in a very short time[15].

2.3.3 Nanojet Technology

Nanojet is mostly used technology, in which high pressure of force is applied to passes the suspension which is separated into at least two sections and that are impact with each other due of high shear forces produced all through the process it marks to reduce of particle size [16].

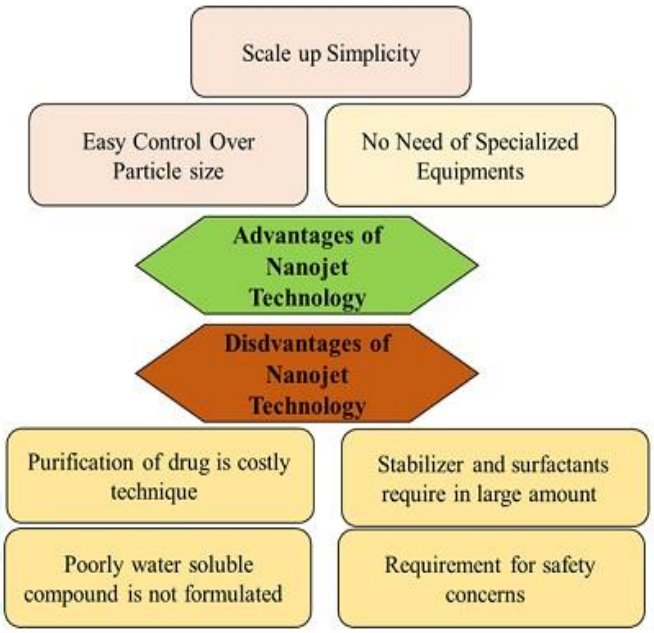

Figure 3 : Advantages and Disadvantages of Nanojet Technology

3 Emulsification-Solvent Evaporation Techniques

By emulsification technique, nanosuspension is prepared by a solution of drug followed and on the other handliquid that is present in non-solvent for drug, then solvent will evaporate and results in precipitation of the nanosize of the drug [15].

4 HydrosolTechnique

It is same as like emulsification solvent evaporation approach. The difference is that in which drug solvent is totally miscible in drug anti- solvent. High shear forces can face the challenges like ostwald ripening and crystal growth. It ensures that, the precipitate which is remaining is smaller in size [17].

5. Supercritical Fluid Method

There are several techniques which are used for the preparation of various formulations like solvent evaporation, solvent diffusion, and organic phase separation but these methods are hazardous to health as well as environment. So facing this challenge, researchers investigated supercritical technology which is eco-friendly. These techniques like supercritical anti solvent, precipitation with compressed antisolvent process (PCS), and rapid expansion supercritical solution (RESS). In this process, liquid solvent should be used (methanol), because solute is not soluble in supercritical fluid so liquid solvent can play a vital role and micronized the solute particles, then nanoparticles are formed. Dexamethasone phosphate drug nanoparticles and Griseofulvin were prepared by this technique.Evaporation of

extracted solvent, diffusion of solvent and separation of organic phase are generally used in preparation of conventional methods[18].

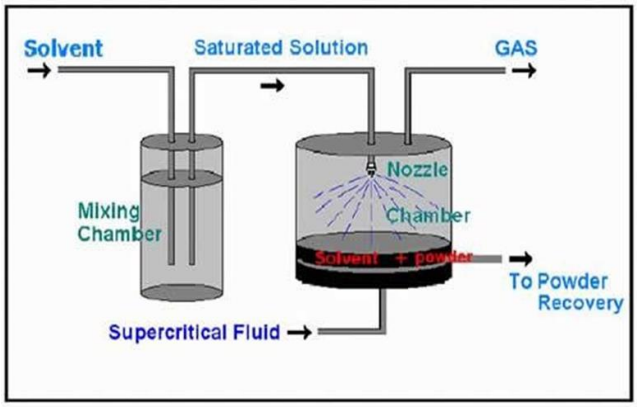

Figure 4: Super Critical Fluid technique [18]

5 Precipitation Technique

This process is carried out by precipitation. In this drug dissolved in solvent(organic) which is water soluble to make surfactant solution after some time drug will show low solubility and result in precipitation on the hand, homogenization with pressure is also helpful here,due to high pressure production of precipitation will enhance and reduce the particle size, which result in higher bioavailability and solubility [19].

6 Dry-co-Grinding

As the name indicates, grinding is done in this technique which helps to improve the surface polarity of drugs. This method is mostly used due to simple and cheap and without using any organic solvent. Properties such as physiochemical and dissolution of low (poor) water soluble drugs can be enhanced by co-grinding [20].

CRITERIA FOR SELECTION OF DRUG (NANOSUSPENSIONS)[21]

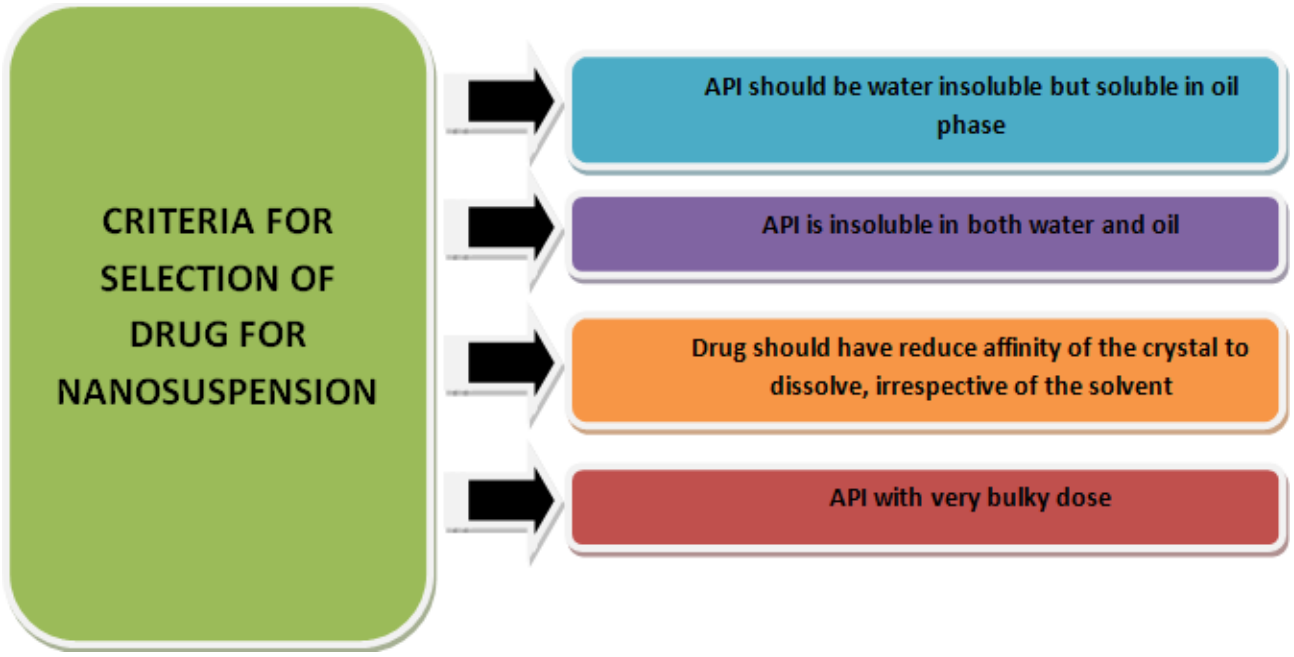

Figure 5: Selection Criteria for Nanosuspension[21]

CHARACTERIZATION OF NANOSUSPENSIONS

Characterization of nanosuspensions is done by various methods with different parameters like size of particles, particle size distribution and also zeta potential, because these parameters are mainly affect on safety, efficacy and stability of formulation. Dissolution profiles are also affected due to solid state of nanoparticles. Thus, the characterization of nanosuspension can play a very crucial role in focussing in vitro and in vivo performance of nano drug delivery. In vivo pharmacokinetic and therapeutic effect of this formulation is mainly depend on particles size, size distribution, the charge on particle and also the crystalline nature of particles.

Particle Size

Particle size and polydispersity index is one the most crucial parameters of nanosuspensions. The size of particles determines the various characteristics of nanosuspensions[11]

- The rate and extent of drug(bioavailability)
- Physicalstability
- Dissolutionrate
- Drug saturationsolubility

The Noyes and Whitney equation showed, when the particles size reduces, the surface area of the particles, solubility and dissolution rate of drug will increase [22,23].

Photon Correlation Spectroscopy (PCS)

This technique (PCS) is widely used to measure the particle size and also called as dynamic light scattering spectroscopy. PCS is capable to accurate measurements of particle sizes in range of 3 nm to 3 μm. However, this technique is not accurate when particles size is above 3 μm[11,24]. In this technique, the brownian motion (movement in random

direction) of particles is measured as a function of time. Laser Diffraction (LD) is typically used to measure particle size range of 0.05–80 μm up to 2000 μm. This technique can also be used to detect and quantify particle size ranges during the production procedure, other techniques routinely used for measuring particle size are optical and electron microscopy. Scanning Electron Microscopy (SEM) [25,26]. Atomic ForceMicroscope (AFM) [27]and Transmission Electron Microscopy (TEM)[28] are also routinely used to characterize nanoparticles size and morphology. Furthermore, the Coulter Counter analysis can be used to determine the absolute number of particles per unit volume for different particle sizes.Other techniques such as Nanoparticle Tracking Analysis (NTA)[29] and Flow Field Flow Fractionation (FIFFF) are example of size analyses of nanoparticles[30].

Particle Morphology and Crystalline State

The high energy amorphous form of drugs is thermodynamically unstable and changes during storage. The amorphous form is preferred due to superior dissolution characteristics and consequently higher bioavailability of the drug[31].Before formulating thenanosuspensionthemajorthing isthetransformation of amorphous to the crystalline state. In order to investigate amorphous and crystalline fractions X-ray powder diffraction is used. XRPD is sometimes considered to be the most appropriate method for evaluating drug with crystalline structure, since each crystal has a specific diffraction pattern [32].However, it should be taken into consideration that there is a slight difference in the crystal structure of the same drug as observed by Tian, who studied the crystalline forms of carbamazepine[33]. Terahertz spectroscopy is a relatively new analytical method used to evaluate crystalline form of drugs where each crystalline polymorph form exhibits specific terahertz absorption spectrum[34,35]. Differential Scanning Calorimetry (DSC) is another commonly used technique for determining crystalline and amorphous fractions. It measures the temperatures and heat flows associated with the transition in drugs from crystalline to amorphous state as a function of time and temperature in a controlled atmosphere. DSC can also be used in conjunction with XRPD[36,37].

Particle Charge (ZetaPotential)

The main role of particle size in nanosuspension is vital to ensure stability of nanosuspension. The electric charge on a particle surface provides electrostatic repulsion between the nanoparticlesand prevents particles from aggregation and precipitation, it provides an illustration of the electric double layer around a charged particle. The double layer consists of a stern layer and a diffusion layer of opposite ions. The electric potential at the shear plane is known as the zeta potential[38]. It is considered that a minimum zeta potential of 30mV is required to ensure pure electrostatic stabilisation. When electrostatic stabilisation is combined with steric stabilisation (by using appropriate polymers), zeta potential of 20mV could be sufficient to prevent drug particles from aggregation and precipitation. Steric stabilisation is defined as stabilisation caused by the adsorbed and hydrated polymer layers on the dispersed particle[39]. Particles charge is typically determined by measuring electrophoretic mobility upon application of an electric field which is then converted to zeta potential by using the Helmholtz-Smoluchowski equation [40].The zeta potential can also be measured by applying an ultrasound wave which induces and called electroacoustic phenomena [41].

Stability

Reduction in particle size results in increased surface energy due to the greater number of unstable surface atoms and molecules. Therefore, the use of stabilisers is often necessary to avoid the cluster making of particle and reduce the chances for Ostwald ripening [42]. Mixture of surfactants and polymers has been found to be beneficial for long-term stabilisation of nanosuspensions [43,44,45]. Polymeric materials and surfactants act as an ionic barricade(barrier). Surfactants can increase the electrostatic repulsion and improve particle stability by altering the zeta potential[46]. Precipitation of particles is another phenomenon that should be taken into account when considering stability of nanosuspensions. According to Stoke's law, reducing the size of particle and decresing the density difference of solid phase, which result an increasing the medium's velocity and decrease the precipitation velocity.

$V = 2r2\ (\rho 1 - \rho 2)\ (9\eta)$

Where$V$is the precipitation velocity, $r$is the particle size, $\rho 1$ is themass density of particles, $\rho 2$ is the mass density of fluid and $\eta$is the viscosity of the medium. The stability of nanosuspension system can also be increased by increasing the uniformity of particle sizes by using centrifugation or other techniques to remove larger particles [47].

Common Stabilizer Which are Used in Nanosuspension

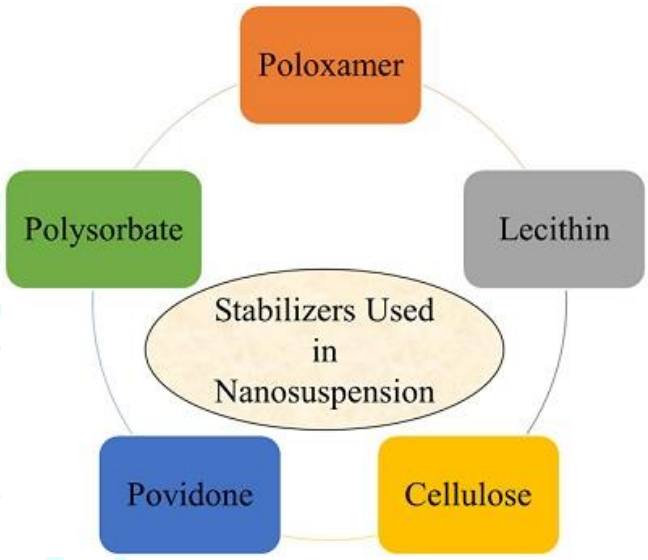

Figure 6: Common Stabilizer Used in Nanosuspension[42]

FORMULATION CONSIDERATION OF NANOSUSPENSION

The preparation of Nanosuspension involves the following agents :

- Stabilizer
- Organicsolvents
- Surfactant
- Co-surfactant
- Otheradditives

Stabilizer

In the absence of stabilizer surface energy of nano-sized particles are too high it can induce agglomeration or aggregation of the drug crystals. In order to yield a physically stable formulation, stabilizers are added which makes the drug particles thoroughly wet and prevents Ostwald's ripening and agglomeration of nanosuspension by providing steric or ionic barriers. Physical stability and in vivo behavior of nanosuspensions depends upon the type and amount ofstabilizers added. In order to obtain a stable

nanosuspension a mixture of stabilizers are required. Polysorbate (Tween/Span series), povidone, cellulosic, poloxamers, and lecithin are some commonly used as stabilizers in the formulation of nanosuspensions [8].

Organic Solvents

Toxicity potential and the ease of their removal from formulation are the two important factors which decide the acceptability of organic solvents in the pharmaceutical area during the formulation of nanosuspension by using emulsion or microemulsion as templates. Ethanol and isopropanol are water miscible solvent, whereas ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol are partially water-miscible, less hazardous and pharmaceutically acceptable [23].

Surfactants

For improving the dispersion in a formulation surfactants are incorporated which perform their action as wetting or deflocculating reducing the interfacial tension. Being of surfactant in the formulation, reduces the interfacial tension [18].

Co-Surfactants

The influence of cosolvent sould be monitored for selected nanosuspension composition, which depends on various factors like uptake of the internal phase and drug loading [8]. After going through the literature it describes certain co-surfactants for various stabilizers can be safely used in the formulation of microemulsion, co-surfactant such as salts (dipotassium glycerrhizinate) can be safely used with stabilizers like transcutol, glycofurol, ethanol, and isopropanol [48].

OtherAdditives

Different type of additives are used in the formulation of nanosuspensions such as, osmogent, cryoprotectant, polyols, buffers and salts which depends upon either the route of administeration or properties of the drug moiety[23].

APPLICATIONS OF NANOSUSPENSION

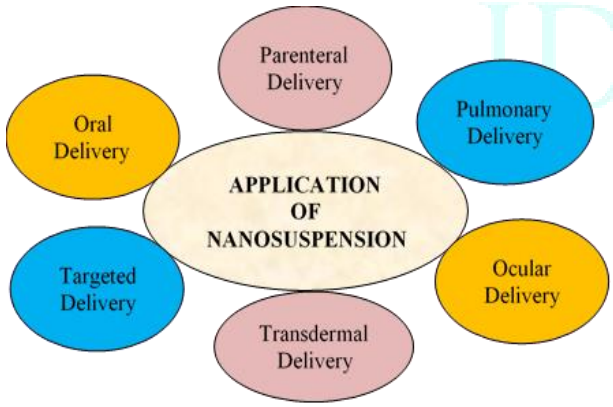

Figure 7: Applications of Nanosuspension

ORAL DRUG DELIVERY

In the conventional dosage form (i.e oral drug administration) there are number of problem such as solubility is poor, inadequate dissolution and does not have sufficient efficacy. To overcome these problem oral nanosuspension is used, particle size should be very small and large surface area as compare to conventional which help to increase the bioavalibility and solubility of poorly soluble drugs(BCS class-II).Advantages of Nanosuspension like high drug loading, enhanced solubility, enhanced stability (physical and chemical) and enhanced bioavailability**.** With the help of simple manufacturing techniques Nanosuspension can be easily incorporated in to numerous dosage forms such as tablets, capsules[49].Recently, Jeong et al developed a new celecoxib (CXB)- loaded nanosuspensions, various nanosuspensions were set up with different polymers and surfactants utilizing a wet media milling methods, therefore determined the particle size. The pharmacokinetic results of prepared formulation are compared with powder form of same drug. The nanosuspension under the appropriate conditions showed the particle size 190 nm, which is increas physical stability (8 week). This Nanosuspension showed higher plasma concentrarion and AUC rate which is compared with powder form of conventional product. Therefore nanosuspension form of CXB- loaded is increase stability and oral bioavailability[50].

PARENERTAL DRUG DELIVERY

In this day and age, number of methods are available to incerase solubility such as solubilization, vesicular system, salt formation, cyclodextrin complexation, but these method have many problemlike cost of manufacturing process, acceptability of parentaral and solubilization capacity, therefore nanosuspension technology is used to solve above problems. It also help to enhance the efficacy of drugs by parental route. Paclitaxel nanosuspension play an important role to control or reduce the risk of median tumor burden [4]. Wang and his co-workers devlopedEtoposide loaded on bovine serum albumin nanosuspension by high pressure homogenization technique. The partical size and drug loading was attended 182,3 nm and 86.49% respectively. The in vitro release profile showed sustained release properties of etoposide. Hence after studies the tissue distribution showed increased concentration and AUC of etoposide in liver, spleen and lung but reduced in kideny and hearth when campared with injection form of same drug [51].Tain et al fabricatedp-terphenyl derivative (H2) by combining microfluidization and precipitation techniques which is formed dry powder by lyophilization method. The results of prapared nanosuspension showed 201.7±5.87nm particle size with increased the solubility of drug (1.46ug/ml) and accelerated dissolution profile [52].

TARGETED DRUG DELIVERY

Nanosuspensions can play a very crucial role in targeting a particular organ which is affected by any disease or disorder. It can also easily change the in vivo behaviour of stabilizer. By phagocytic system drug will be engulfed and it is responsible for targeting a specific site. Various targeting formulation are available such as antifungal, antimicrobial, antileishmanial and etc[48]. Abraxane™ established a clinical standard of paclitaxel which is approved by FDA. Paclitaxel is used for treatment of cancer. Yin et al devloped Paclitaxel loaded nanosuspension based on human serum albumin with poly ethylene glycole (PEG) to optimize pharmakokinetics, safety and in vitro biodistribution (PTX-PEG-HSA). Result of in vivo pharmacokinetics showed prolonged plasma circulation [53]. Hong and co-workers prepared FA-modified ACGs nanosuspensions. Annonaceous acetogenins are a biggest family of fatty acid which is derived from natural products and related to Annonaceae species, It showes anticancer and biological activity. The poorly solubility and toxicity restrict their clinicaly application. Therfore, modified β-cyclodextrin with folic acid then mixed with soybean lecithin to prepare FA-modified ACGs nano-suspensions. The prepared nanosuspension with 199.5 nm average particle size and 57.59% loaded capacity and showed within 142 hours sustained release. Hence in vivo studies showed enhance cytotoxicity and less toxicity in 4T1

tumor bearing mices [54].

OCULAR DRUG DELIVERY

Nanosuspension is also used for ocular drug delivery to sustained the release of drug. Liang and Binner formulated cloricromene nanosuspension for ophthalmic (ocular) delivery using Eudragit. This work showed higher availability of drug in aqueous humor of rabbit eye. Thus, Various formulation of Nanosuspension offers a favorable tissues for enhancing the bioavailability as well as shelf life of drug after ophthalmic application [41].For the treatment of ocular disease several advance techniques and various drug delivery systemhave been suggested. The importent factors which are effect in the success of ocular therapy such as development of safe, effective, economic and non-invasive new drug delivery systems. These speciale non-invasive ocular delivery systems are targeted drug delivery to the ocular tissues by reducing doses and toxicity which arecampared with the conventional formulations. Non-invasive systems are prapared with encompassing biodegradability, biocompatibility, mucoadhesion, solubility and permeability enhancement ingredients[55].In addition, nanosuspension of triamcinolone acetonide showed significant potential such as increase loading capacity, release profile and solubility properties. The size of nanosuspenstion is suitable for topical ocular drug delivery system [56]. The studies done by Ambhore et al showed the drug is formulated with surfactant and polymer its effect on particle size and drug release. Sparfloxacin prepared with HPMC and chitosan by solvent diffusion technique which is followed by probe sonication. The prepared nanosuspention after characterizetion showed 300 to 500 nm average particle size, suitable shape, zeta potential and drug release profile [57].

PULMONARY DRUG DELIVERY

For pulmonary delivery, mechanical or ultrasonic nebulizers are the technique which is, nanosuspensions are nebulised. All the aerosol droplets contain drug nanoparticles due to the presence of small particles. There are various drugs which are successfully tried with pulmonary route such as budesonide, p53 gene, ibuprofen, nifesipine, and ketotifen etc [58].Coenzyme Q_{10} is an antioxidant substance which is indicated as a dietary supplement and proposed as adjuvant in the management of cardiovascular disorders and tumor for its protective and immunostimulating activities. CoQ_{10} nanosuspension designed and administreted to the lungs by nebulization. CoQ_{10} is stabilized by surfactants, such as lecithin, PEG32 stearate and vitamin-E TPGS. Particle size range of nanosuspension of $CoQ_{10}$is 35-60 nm, the smallest particles size allowed to delivered the drug to the lungs [59].

TRANSDERMAL DRUG DELIVERY

Flurbiprofen (FB) isone of the non-steroidal anti-inflammatory drugs (NSAIDs) it is low water soluble. Nanonization is a technique which is converting the drug particle in to nano size. Recently, design of experiment (DoE) approaches used to develop novel formulations of nanosuspensions. Plantacare is as stabilizer using in DoE experiment approaches to evaluate the critical formulation attributes (CFAs) and critical process parameters (CPPs). For dependent variable particle size, particle size distribution and zeta potential values were selected while FB%, FB: PL and homogenization cycles were independent variables. The solubility study of nanosuspensions comparison with the coarse powder and physical mixture. The in vitro permeation of FB nanosuspension andsolution were determined by dialysis bag membrane and rat skin. The particle size (665 nm-700nm), polydispersity index (0.200-0.300) and zeta potential values (-30 mV) were found. FB nanosuspension observed with spherical shape and crystalline stracture. The solubility of FB was 5.3 fold increased in nanosuspension formulation and permeability of FB formulation was higher than FB solution in rat skin. Therfore DoE design is a useful design to prepare FB nanosuspensions, result is to improve water solubility and permeability of skin of BCS Class II drugs [60].The slow permeation of many drugs across the skin layer is the main disadvantages of transdemal route. There are several techniques to cross the skin barrire, such as penetration enhancers in topical formulation for example diethylene glycol monoethyl ether included in new declofinac. The in vitro permeation studies performed by Pireddu et al reported nanonizing is as a main factor for dermal permeation of topical diclofenac formulation. Nanosuspension of diclofenac with diethylene glycol monoethyl ether increase the skin permeation of drug across the skin [61].

CONCLUSION

Initially, nanosuspension technology came to solve problem of solubility of poorly soluble drugs. As information was attained by applications, nanosuspension solved poor solubility and bioavailability problem of hydrophobic drugs.Fabrication methods like media milling and high pressure homogenizer are utilized for large scale fabrication of Nanosuspensions. Nanosuspensions can be administered via parenteral, oral, pulmonary, ocular and topical routes. This is a major advantage of nanosuspension technology to obatin final drug formulation in various forms with patient complience.Since nanotechology is simple, cost-effective and devloped in a lab scale. Nanosuspensions canincrease dissolution velocity and saturation solubility several poor bioavailability drugs. Any devloped drug delivery system requires safety, efficiency and stability. Moreover, the safety and efficiency depended on the stability in some cases. A good stability of a formulation is a warranty for a reliable safety and efficiency. Therefore, the stability issue of nanosuspensions in drug delivery is a very important and critical aspect of this technology. Although, nanosuspensions technology has been studied tremendously in laboratory scale, its application on pharmaceutics industrial is still restrained. The stability issue of nanosuspensions has been highlighted as major problem for this.According to our notion, upcoming era will emerge in which soluble drugs will be intentionally converted to insoluble complexes to take advantage of the benefits conferred by nanosuspension drug delivery.

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