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Nanosuspension -A Novel Approaches In Drug Delivery System

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The interest in the preparation and application of nanometer-sized materials is increasing due to their tremendous potential as a drug delivery system with wide range of applications. Recently, nanoscale systems have received much interest as a way to resolve solubility issues because of their cost-effectiveness and technical simplicity compared to liposomes and other colloidal drug carriers. Nanosuspensions have proven to be a better alternative over other approaches currently available for improving bioavailability of number of drugs with low solubility. Nanosuspensions have been extensively developed for a wide range of drugs and have been evaluated for in vitro and in vivo applications by various routes: parenteral, oral, pulmonary, topical. They have also been used for drug targeting. Different preparation methods for nanosuspensions and their application are being reported and patented. In fact, the number of products based on nanosuspension in the market and under clinical study is higher than that of other nanotechnology-based applications. A surprisingly large proportion of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These so-called 'brickdust' candidates can now be rescued by formulating them into crystalline nanosuspensions.

Keyword: Nanosuspensions, Bioavailability, Drug Discovery, Site Specific Delivery

1. INTRODUCTION: A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non-oral use. The absorption of drugs from the intestine is mainly dependent on their solubility in the intestinal fluids and their intestinal membrane permeability. Insufficient

absorption of poorly soluble drugs is mainly due to slow dissolution and the generation of a small concentration gradient across the intestinal mucosa. To overcome these problems different formulations of nanosized drugs have been developed. Nanosuspensions are colloidal dispersions of solid drug particles in a liquid phase with average particle sizes below 1 µm stabilized by the use of surfactants. Solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. Nanosuspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. These are simple to prepare and are more advantageous than other approaches. Techniques such as wet milling, high-pressure homogenization, emulsification-solvent evaporation and super critical fluid have been used in the preparation of nanosuspensions. It has the advantage of delivery by various routes, including oral, parenteral, pulmonary and ocular routes. The present article reviews the current methods used to prepare nanosuspensions and their application in drug delivery. Nanosuspensions are 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 µm in size.[9] 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 (e.g., oral or intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that 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. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries.

CLASSIFICATION OF SUSPENSION

I. Based On General Classes

o Oral suspension
o Externally applied suspension
o Parenteral suspension

II. Based On Proportion Of Solid Particles

o Dilute suspension (2 to10%w/v solid)
o Concentrated suspension (50%w/v solid)

III. Based On Electrokinetic Nature Of Solid Particles

o Flocculated suspension
o Deflocculated suspension

IV. Based On Size Of Solid Particles

o Colloidal suspension (< 1 micron)
o Coarse suspension (>1 micron)
o Nano suspension (10 ng)

The nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix. Apart from this, it has all other advantages of a liquid dosage form over the solid dosage forms. The present review is focused on various methods of preparing nanosuspensions, critical parameters to be characterized and the application of nanosuspension formulations. Most of the drugs are not soluble in water and they create major problem during formulation they also show poor bioavailability. Reduction in particle size of such drugs enhances the dissolution rate and bioavailability. Nano suspension a promising delivery used to enhance the solubility of hydrophobic drugs. Media milling and high pressure homogenization technique are used commercially to produce nano suspensions. Recently emulsion and micro emulsion as templates are used to produce nano suspension. They are administered by Parenteral,

per oral, ocular and pulmonary routes. Now their application also extended to site specific delivery. This review describes the methods of pharmaceutical production, formulations and pharmaceutical applications in drug delivery as well as the marketed products. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion.

2. Advantages

- Suspension can improve chemical stability of certain drug.
- Drug in suspension exhibits higher rate of bioavailability than

Other dosage forms bioavailability is in following order,

Solution > Suspension > Capsule > Compressed Tablet

- Duration and onset of action can be controlled.
- Suspension can mask the unpleasant/ bitter taste of drug.

3. Disadvantages

- Physical stability, sedimentation and compaction can causes problems.
- It is bulky sufficient care must be taken during handling and transport.
- Uniform and accurate dose cannot be achieved unless suspension are
- In a proper dose.

Features Desired In Pharmaceutical Suspensions

- The suspended particles should not settle rapidly and sediment produced must be easily re-suspended by the use of moderate amount of shaking.
- It should be easy to pour yet not watery and no grittiness.
- It should have pleasing odour, colour and palatability.
- Good syringeability.
- It should be physically, chemically and microbiologically stable.
- Parenteral/Ophthalmic suspension should be sterilizable.

4. Applications

- Suspension is usually applicable for drug which is insoluble or poorly
- soluble.
- To prevent degradation of drug or to improve stability of drug.

5. CLASSIFICATION

There are three general classes of pharmaceutical suspensions:

- Orally administered (sometimes referred to as mixtures)
- Externally applied (topical lotions)
- Injectable(parenteral)

a. ORAL SUSPENSIONS

The suspensions contain relatively high amounts of suspended material for oral administration. The vehicle may be syrup, a sorbitol solution, or a gum-thickened, water-containing artificial sweetener because in addition to ingredients, safety, taste, and mouth feel are important formulation considerations. In the case of limited shelf life (low chemical stability of the insoluble drug), the dosage form may be prepared as a dry granulation or powder mixture that is reconstituted with water prior to use.

b. TOPICAL SUSPENSIONS

Historically, the externally applied ‘‘shake lotion’’ is the oldest example of a pharmaceutical suspension. The protective action and cosmetic properties of topical lotions usually

require the use of high concentrations of the dispersed phase, often in excess of 20%. Therefore, topical lotions represent the best example of suspensions that exhibit low settling rates. Various pharmaceutical vehicles have been used in the preparation of topical lotions, including diluted oil-in-water or water-in-oil emulsion bases, determatological pastes, magmas, and clay suspensions. Safety and toxicity are import combination for determatological acceptability. some time, the drug particles settled slowly, forming tightly packed sediment that was almost impossible to resuspend even with vigorous shaking. Primary particles or small aggregates, reaching the bottom of the container during sedimentation (settling), slipped past each other and produced compact layers of solids. The inter particle interaction in such compact sediments is relatively high because the inter particle distances are small, and the weak van der Waals forces of attraction. Such conditions frequently lead to the undersirable phenomenon of ‘‘caking or claying’’ and require extensive agitation for resuspension. The physical instability of these early deflocculated suspensions led to other methods of producing physically stable pharmaceutical suspensions.

Deflocculated suspensions are produced by three methods

1) Mutual repulsion to large z-potential.

2) Adsorption of a smaller hydrophilic or lyophilic colloid on larger suspended particles.

3) Steric hindrance due to adsorption of an oriented non-ionic surfactant or polyelectrolyte.

c. FLOCCULATED SUSPENSIONS

Matthews and Rhodes, Haines and Martin and Ecanow and co-workers are credited with establishing the ‘‘structured particle’’ concept or flocculated pharmaceutical suspension. The following figure explains different term like flocculation, agglomeration, and coagulation. The term aggregation can apply to all three. Flocculation refers to the formation of a loose aggregation of discrete particles held together in a network like structure by physical adsorption of macromolecules, bridging during. chemical interaction (precipitation) or when the longer-range van der Waals forces of attraction exceed the shorter-range forces of repulsion. The floccule referred to as a ‘‘stable loc’’ usually contains varying amounts of entrapped liquid medium or vehicle within the network like structure Flocculated pharmaceutical suspensions are prepared using several methods. The choice depends on the properties of the drug and the class of suspension desired. A stable flocculating may also be produced by dispersing insoluble particles in a turbid or hazy vehicle consisting of finely dispersed or emulsified semi polar, liquid droplets, which cause the droplets to be adsorbed on the surface of the insoluble drug particles, resulting in a stable floc. Turbid aqueous vehicles have been prepared by the interaction of non-ionic surfactants and preservatives. The concentration of surfactant and preservative required for haze formation may be reduced by the addition of small amounts of sorbitol to the vehicle.

6. UTILITY OF SUSPENSIONS

A suspension is often chosen as pharmaceutical dosage form for drugs insoluble in water and aqueous fluids at the dosage required for administration and when attempts to solubilize the drug would compromise stability and safety. For oral administration, the taste of a bitter or unpleasant drug can often be masked by choosing an insoluble form of the active drug. An aqueous suspension is a useful oral dosage form for administering insoluble or poorly soluble drugs. The large surface areas of the dispersed drug particles often facilitate absorption. Unlike drug particles contained in tablets or capsules, the dissolution of drug particles in suspension and subsequent absorption commence upon dilution in gastrointestinal fluids. Finely divided particles

dissolve faster and have higher relative solubility than do similar macro particles. The parenteral suspension is an ideal dosage form for prolonged or ‘‘depot’’ release. In the administration of a drug as an aqueous or oleaginous . suspension into subcutaneous or muscular tissue, the drug is deposited at the injection site. The depot acts as a reservoir, slowly releasing drug at a rate related to both the intrinsic aqueous.

7. NANOSUSPENSION-AN APPROACH TO ENHANCE SOLUBILITY OF DRUGS

In recent years, there has been a considerable interest in the development of novel drug delivery systems using particulate delivery systems like nanoparticles. Nanoparticles represent a promising drug delivery system of controlled and targeted release. In this context, nanosuspensions will be effective in increasing the solubility, bioavailability of poorly soluble drugs. The review focuses on advantages, method of preparation, physical characteristics and evaluation of nanosuspensions. A large proportion of new chemical entities coming from drug discovery are water insoluble, and therefore poorly bioavailable, leading to hurdles in formulation development efforts. There are number of formulation approaches like micronisation, solubilization using cosolvents, precipitation techniques etc., to resolve the problems of low solubility and low bioavailability. Each of them have their own limitations. Other techniques like micro emulsions, solid dispersions and inclusion complexes using cyclodextrins even though showed increased solubility, but not applicable for drugs which are insoluble in both aqueous and organic media. The next development stepis transformation of the micronized drug to drug nanoparticles and nanosuspensions. Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance. Nanosuspension technology offers novel solution for these poorly soluble drugs. Nanosuspension consists of pure poorly water soluble drugs with or without any matrix material suspended in dispersion. They can be surfactant free; can also comprise surfactants or stabilizers or both. 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. Nanosuspensions are distinctive and commercially feasible approach to solve the problems of hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nanosuspensions for various routes of administration**.** More than 40 percent of the drugs coming from High-through output screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms.

One of the critical problems associated with poorly soluble drugs is too low bioavailability and or erratic absorption.
These techniques for solubility enhancement have some limitations and hence have limited utility in solubility enhancement. Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} meters. The present article describes the details about nanosuspensions.

Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. The review article includes the methods of preparation with their merits and demerits, characterization and evaluation parameters. A nanosuspension not only solve the problems of poor solubility and

bioavailability but also alter the pharmacokinetics of drug and thus improves drug safety and efficacy.

8. NANOSUSPENSION-A PROMISING TOOL FOR DRUG DELIVERY SYSTEM

Nanosuspension can be defined as a biphasic system consisting of pure drug particles dispersed in a aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. Nanosuspension consist of the poorly water soluble compound without any matrix material suspended in dispersion Need for Nanosuspension Most of the drugs coming from high-screening are poorly water soluble. Formulation of poorly water soluble drug is always being a challenge. One of the major problem associated with them is low bioavailability due to less absorption. This problem can be overcome by using nanosuspension . Bottom up Technology In Bottom up technology the drug is dissolved in a solvent, which is then added to non-solvent that causes precipitation of the fine drug particles. Simple and low expenditure. In this technique, the drug needs to be soluble in at least one solvent which is miscible with nonsolvent. Media milling In this method the nanosusensions are produced using high-shear media mills or pearl mills. Milling chamber consist of Milling chamber Milling shaft Recirculation chamber Process is done under controlled temperature. Advantages Disadvantages Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity. Nanosuspensions contaminated with materials eroded from balls may be problematic when it is used for long therapy. The media milling technique is time consuming. Some fractions of particles are in the micrometer range. Scale up is not easy due to mill size and weight 8 Media milling.Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Most of the cases require multiple passes or cycles through the homogenizer. Homogenization Advantages Disadvantages It does not cause the erosion of processed materials . Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity . It is applicable to the drugs that are poorly soluble in both aqueous and organic media. It allows aseptic production of nanosuspensions for parentral administration. Preprocessing like micronization of drug is required. High cost instruments are required that increases the cost of dosage form .Conclusion Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form.

9. ADVANTAGES OF NANOSUSPENSION

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting

10. PREPARATION OF NANOSUSPENSION

The most common approach that has been used for preparing nanosuspensions is micronization by colloid or jet milling. [10] This method increases the dissolution rate of the drug but does not have any impact on the saturation solubility and thus cannot improve the bioavailability of drugs.Sucker and co-workers used a precipitation technique to produce nanoparticles by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle. [8] This has the advantage of using relatively simple and low-cost equipment. However, this created problems in stirring and mixing when taken up for large-scale production. The major challenge of this technique is to avoid

crystal growth that occurs on storage due to Ostwald ripening.The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods: (a) wet milling, (b) homogenization, (c) emulsification-solvent evaporation and (d) supercritical fluid method.

a. Wet milling

Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction.The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. Planetary ball mills (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) is one example of an equipment that can be used to achieve a grind size below 0.1 µm. A nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling technique. The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5 µm.

b. Homogenization Dissocubes

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Dissocubes was developed by Muller et al. in 1999. In this case, the suspension of the drug is made to pass through a small orifice that results in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size and the required homogeneity. This principle is employed in the APV Gaulin Micron LAB 40 Homogenizer (APV Homogenizer, Lóbeck, Germany) and the NS 1001L-Panda 2K high-pressure homogenizer (Nirosuavi. S.P.A., Parma, Italy).Scholer et al. prepared atovaquone naanosuspensions using this technique. An aqueous suspension of atovaquone was dispersed using an Ultra turrax T25, IKA-Werke GmbH& Co. KG, Staufen, Germany and was further homogenized in a Gaulin Micron Lab 40 high-pressure homogenizer. After subjecting to pressures of 1.5 x 10^7 (two cycles), 5 x 10^7 (two cycles) and 1.5 x 10^8 (20 cycles) Pa, a nanosuspension of atovaquone with a mean diameter of 279 ± 7 nm and mean polydispersity index of 0.18 ± 0.001 was obtained. To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. The major advantage of high- pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.

c. Nanopure

Nanopure is suspensions homogenized in water-free media or water mixtures. In the Dissocubes technology, the cavitation is the determining factor of the process. But, in contrast to water, oils and oily fatty acids have very low vapour pressure and a high boiling point. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by high- pressure homogenization mention that higher temperatures of about 80□C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 0□C or even below the freezing point and hence are

called "deep-freeze" homogenization. The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substances at milder conditions.

d. Nanoedge

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology. In this technique, the precipitated suspension is further homogenized, leading to reduction in particle size and avoiding crystal growth.Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in the formulation. For an effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be included to provide a solvent-free modified starting material followed by high-pressure homogenization.

e.Nanojet-technology

This technique, called opposite stream or nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Equipment using this principle includes the M110L and M110S microfluidizers (Microfluidics). Dearn prepared nanosuspensions of atovaquone using the microfluidization process. The major disadvantage of this technique is the high number of passes through the microfluidizer and that the product obtained contains a relatively larger fraction of microparticles.

f.Emulsification-solvent evaporation technique

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

g.Hydrosol method

This is similar to the emulsification- solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

h. 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. Young et al. prepared cyclosporine nanoparticles in the size range of 400-700 nm using this process. In the PCA method, the drug solution is atomized into a chamber containing compressed CO_2. As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti- solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals. Nanoparticles of griseofulvin, a drug with poor solubility, were prepared by Chattopadhyay et al. using this method. [16] 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 supersaturation, which may also result in the

development of an amorphous form or another undesired polymorph.

11. PHARMACEUTICAL APPLICATION

Oral Drug Delivery

Poor solubility, incomplete dissolution, and insufficient efficacy are the major problem of oral drug administration. Due to smaller particle size and much larger surface to volume ratio, oral nanosuspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs. In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugsThe nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubject variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into various dosage forms like tablets, capsules, and fast melts. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours.

Parental Drug Delivery

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve the above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden. Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in Mycobacterium avium-infected female mice. Rainbowet al. showed that intravenous nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation.

Pulmonary Drug Delivery

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery. Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small. Different types of nebulizers are available for the administration of liquid formulations. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.

Ocular Drug Delivery

Nanosuspensions are used in ocular delivery of the drugs for sustained release. Liang and co-workers prepared cloricromene nanosuspension for ocular delivery using Eudragit. Experiment showed higher availability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation offers a promising way of improving the shelf-life and bioavailability of drug after ophthalmic application.

Targeted Drug Delivery

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter in vivo behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly. Kayser formulated an aphidicolin nanosuspension that improved the drug targeting to macrophages which were Leishmania infected. He stated that the drug in the form of nanosuspension had EC_{50} of 0.003 µg/ml, whereas the conventional form had 0.16

µg/ml.Scholer et al. described an enhanced drug targeting to brain in the treatment of toxoplasmic encephalitis using an atovaquone nanosuspension.

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. The oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with just 44.7 mg-h/l for naprosyn suspensions and 32.7 mg-h/l for anaprox tablets. Oral administration of the gonadotrophin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%. A nanosuspension of Amphotericin B developed by Kayser et al. showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation.

Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension 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 nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min). Kocbek et al.showed a significant improvement in the dissolution rate (65% in 10 min) of Ibuprofen made as a lyophilized nanosuspension powder as compared with (<15% in 10 min) that of the micronized drug. The ocular anti-inflammatory activity of Ibuprofen-Eudragit RS100 nanosuspensions was greatly improved when compared with an aqueous solution of Ibuprofen lysinate. Further, the aqueous humor drug concentration was significantly higher in groups treated with Ibuprofen-Eudragit RS when compared with the Ibuprofen- treated group. Langutth et al. showed a nearly 5.7- fold increase in the AUC for spiranolactone, a low solubility drug made as a solid lipid nanoparticle. Dissocubes type showed about 3.3-fold increase in the AUC. They observed that the improvement in drug solubility in the intestine as well as in the dissolution rate of spiranolactone is the most likely mechanism for the increase in the AUC.

Intravenous administration

The parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug. It is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or degraded in the GIT. One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages.Peters et al. prepared clofazimine nanosuspensions for IV use and showed that the drug concentrations in the liver, spleen and lungs reached a comparably higher level, well in excess of the minimum inhibitory concentration for most Mycobacterium avium strains. Further, the study also indicates that the nanoparticle formulation accumulated more in the liver than the liposomal formulation, indicating a better targeting potential of the nanoparticle formulation. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as use of surfactants, cyclodextrins, etc., to improve bioavailability. A stable intravenously injectable formulation of omeprazole has been prepared to prevent the degradation of orally administered omeprazole.

Pulmonary administration

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug

particle is contained, leading to a more uniform distribution of the drug in lungs. They also increase adhesiveness and thus cause a prolonged residence time. Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer. The pharmacokinetics of the nebulized nanocrystal budenoside suspension showed comparable AUC, higher Cmax and lower Tmax as that of the pulmicort respules. Other applications include ocular delivery of the drugs as nanosuspensions to provide a sustained release of drug. Pignatello et al.prepared Eudragit retard nanosuspensions of cloricromene for ocular delivery. They observed that the drug showed a higher availability in rabbit aqueous humor and the formulation appeared to offer a promising means of improving the shelf-life and the bioavailability of this drug after ophthalmic application.

Drug Targeting

Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the in vivobehavior. The drug will be up taken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly. Kayser formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania-infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/ml whereas the nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml. Scholer et al. showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii using a nanosuspension formulation of Atovaquone.

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. [33] The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT, e.g.,Cryptosporidium parvum. Bupravaquone nanosuspensions have been reported to demonstrate an advantage in TRC- alpha-deficient mice infected with Cryptosporidium parvum oocytes. The bioadhesion can also be improved by including a mucoadhesive polymer in the formulation.

12. Evaluation of nanosuspensions

A) In-Vitro Evaluations

1. Particle size and size distribution
2. Particle charge (Zeta Potential)
3. Crystalline state and morphology
4. Saturation solubility and dissolution velocity

B) In-Vivo Evaluation

C) Evaluation for surface-modified Nanosuspensions

1.Surface hydrophilicity
2. Adhesion properties
3. Interaction with body proteins

1) Mean particle size and size distribution

The mean particle size and the width of particle size distribution (called Polydidpersity Index) are determined by Photon Correlation Spectroscopy[30] (PCS). Particle size and polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3nm- 3 µm only. PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability. (Should be close to zero). PCS is a versatile

TABLE-1: Nanosuspension technology over other conventional formulations technologies for poorly soluble drugs

Route of administration	Potential benefits
Oral	Rapid onset Reduced fed/fasted ratio Improved bioavailability
Intravenous	Rapid dissolution Tissue targeting
Ocular	Higher bioavailability More consistent dosing
Inhalation	Higher bioavailability More consistent dosing
Subcutaneous/ intramuscular	Higher bioavailability Rapid onset Reduced tissue irritation

technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD). LD measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force Microscopy[31] is used for visualization of particle shape.

2) Particle charge (Zeta Potential)

article charge determines the stability of nanosuspension. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ±20mV.

Table 2 : MARKETED NANOSUSPENSION FORMULATIONS

Table 2 | **Solid-particulate-nanosuspension-based formulations in development and in the market**

Drug	Indication	Drug delivery company	Pharma company	Route	Status
Paclitaxel	Anticancer	American BioScience	American Pharmaceutical Partners	Intravenous	Phase III
Undisclosed multiple	Anti-infective	Baxter NANOEDGE	Undisclosed	Oral/ intravenous	Preclinical to Phase II
Undisclosed	Anticancer	Baxter NANOEDGE	Undisclosed	Intravenous/ oral	Preclinical to Phase I
Rapamune	Immuno-suppressant	Elan Nanosystems	Wyeth	Oral	Marketed
Emend	Anti-emetic	Elan Nanosystems	Merck	Oral	Marketed
Cytokine inhibitor	Crohn's disease	Elan Nanosystems	Cytokine PharmaSciences	Oral	Phase II
Diagnostic Agent	Imaging agent	Elan Nanosystems	Photogen	Intravenous	Phase I/II
Thymectacin	Anticancer	Elan Nanosystems	NewBiotics./Ilex Oncology	Intravenous	Phase I/II
Fenofibrate	Lipid lowering	SkyePharma	Undisclosed	Oral	Phase I
Busulfan	Anticancer	SkyePharma	Supergen	Intrathecal	Phase I
Budesonide	Asthma	Elan Nanosystems	Sheffield Pharmaceuticals	Pulmonary	Phase I
Silver	Eczema, atopic dermatitis	NUCRYST	Self-developed	Topical	Phase I
Calcium phosphate	Mucosal vaccine adjuvant for herpes	BioSante	Self-developed	Oral	Phase I
Insulin	Diabetes	BioSante	Self-developed	Oral	Phase I

3) **Crystalline state and particle morphology**

Differential Scanning Calorimetry(DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction(XRD) is also used for determining change in physical state and extent of amorphous drug.

4) Saturation solubility and dissolution velocity

The nanosuspension increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific

constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility.

13. CONCLUSION

The nanosuspension can be proved as a gift as the poorly water soluble drugs can be easily formulated into nanosuspension. One of the critical problems associated with poorly soluble drugs is too low bioavailability. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. Nanosuspension not only solves the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Nanosuspensions are sub-micron colloidal dispersions of nanosized drug particles stabilized by surfactants.Nanosuspension drug delivery has obtained great success in the preparation of insoluble drugs. The nanosuspension technology can confer a series of special characteristics to the drugs, such as the enhanced dissolution rate and saturation solubility. This mini review first described the differences between the nanocrystals and nanosuspensions. Next, the product techniques, the stable measures, the special features, and the routes of administration of the nanosuspensions were reviewed and compared. Finally, some existing shortcomings of the nanosuspensions were mentioned and the perspectives of the nanosuspensions were also made.

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