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A Review on Nanosuspension

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Abstract: ***The current article cites the importance and promising future of new age dosage form. Nanosuspensions are defined as submicron collidal dispersions of pharmaceutical active ingredient particles in liquid phase size below 1µm without any matrix material stabilized by surfactants. Solubility plays an essential role in drug effectiveness and oral adminstration. It improves the bioavailability of poorly soluble drugs. So the nanosuspensions are developed to increase the oral bioavailability. Techniques used in preparation of Nanosuspension are the media milling, high pressure homogenization, Precipitation, Supercritical fluid Process, Melt Emulsification, Lipid Emulsion, Emulsification Solvent Evaporation Technique. Polymers used are Hydroxy propyl methyl cellulose, Hydroxy ethyl cellulose. current efforts are made directed to extend applications in site specific drug delivery.***

Keywords: Nanotechnology, Nanosuspensions, Enhanced Bioavailability, Polymers

1. Introduction

- In the current trends Nanotechnology is an emerging field in all Areas of science, engineering and technology. It is a Novel interdisciplinary area of comprehensive research That combines medicine and other life sciences. It offers A potential for unique and novel approaches with broad Spectrum of application in cancer treatment including Areas such as diagnostics, therapeutics and prognosis [1].
- More than 40% of new chemical Entities being generated through drug discovery Programmes are poorly water soluble. The formulation Of poorly water soluble drugs has always been a Challenging problems faced by pharmaceutical Scientists [2]. There are many conventional methods Such as micronization, solubilisation using co-solvents, Surfactant dispersions and precipitation technique has been developed for improving solubility of poorly water soluble drugs [3]. But these techniques show limitations To the drugs which are not soluble in both aqueous and Organic solvents.
- Nanosuspensions are defined as the Submicron Collidal dispersions of pharmaceutical active ingredient particles in a liquid phase, size below 1µm, without any matrix material which are stabilized by surfactants and polymers [4]. An increasing number of newly developed drugs are poorly soluble; in many cases drugs are poorly soluble in both aqueous and organic media excluding the traditional approaches of overcoming such solubility factors and resulting in bioavailability problems. An alternative and promising approach is the production of drug nanoparticles (i. e. nanosuspensions) to overcome these problems.
- Nanotechnology can be used to solve the Problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanosuspension is favored for compounds that are insoluble in water (but are soluble in oil) with high log P Value, high melting point and high doses. Nanosuspension Technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs Such as Atorvastatin, 13 Famotidine, 14 Simvastatin, 15Revaprazan, 16 Aceclofenac, 17 are formulated as Nanosuspension.

Formulation of Nanosuspension [5]

- **Stabilizers**: Wet the drug particles thoroughly: Prevent Ostwalds ripening and agglomeration of Nanosuspension, providing steric or ionic barriers. Eg: lecithins, poloxamers, polysorbates, cellulosics, povidones.
- **Cosurfactants**: Influence phase behavior when Micro emulsions are used to formulate Nanosuspensions. Eg: Bile salts, DipotassiumGlycerrhizinate, Transcutol, Glycofurol, Ethanol, Isopropanol.
- **Organicsolvent**: Pharmaceutically acceptable less Hazardous solvent for preparation of Formulation. eg: Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl Lactate, Triacetin, Propylene carbonate, Benzyl Alcohol.
- **Otheradditives**: According to the requirement of The route of administration or the properties of the Drug moiety. Eg: Buffers, Salts, Polyols, Osmogens, Cryoprotectan.

2. Methods of Preparation of Nanosuspension

Mainly there are two methods for preparation of Nanosuspensions. The conventional methods of Precipitation (Hydrosols) are called 'Bottom up Technology'. The 'Top Down Technologies' are the Disintegration methods and are preferred over the Precipitation methods. The 'Top Down Technologies' Include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and Combination of Precipitation and High-Pressure Homogenization (Nanoedege). [6].

1) Bottom-up technology
2) Top-down technology

1) Top-Down Technology:-

The top down technologies include

a) Media milling

Media 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. [7-10].

b) High Pressure 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 result 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). 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.11-14.

- **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 800C Promoted disintegration, which cannot be used for Thermolabile compounds. In nanopure technology, the drug suspensions in the non-aqueous media were homogenized at 00C 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.15, 16.

- **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.17

2) Bottom Up Technology:-

a) Precipitation Technique (Solvent-Antisolvent Method):-

Precipitation method has been used for long years for the preparation of submicron particles. It is mainly used for the poorly soluble drugs. First drug is dissolved in a suitable solvent. This solution is then mixed with a miscible anti-solvent system in the presence of surfactants. Rapid addition of drug solution in to the anti-solvent leads to the sudden super-saturation of drug in the mixed solution forms ultrafine drug solids. Precipitation method involves two phases-nuclei formation & crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but low growth rate is necessary. Both rates are depending on temperature. In this technique the drug needs to be soluble in at least one solvent which is miscible with non-solvent [18].

- **Supercritical Fluid Process:**

The particle size reduction was achieved more by the solubilization and nanosizing technologies through the super critical fluid process. Super critical fluids (SCF) are noncondensable dense fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). This process allows the micronization of drug particles to submicron level. Recent advances in SCF process are to create nanoparticulate suspension of particle size of 5 to 2000nm in diameter 18. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these

processes restrict the utility of this technology in the pharmaceutical Industry.

b) Melt Emulsification Method:

In this method drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath.

- **Solvent evaporation:**

Here the solutions of polymer are prepared in volatile solvents and emulsions. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. Conventionally, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e. g., oil-in-water (o/w) or double-emulsions, e. g., (water-in-oil)-in-water, (w/o) /w. These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, by continuous magnetic stirring at room temperature or under reduced pressure. The solidified nanoparticles are collected which was washed with distilled water to remove the additives like surfactants, and then it was lyophilized [19].

- **Lipid emulsion/microemulsion template:**

This method applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. Here the drug was dissolved in suitable organic solvent and it is emulsified in aqueous phase using suitable surfactants. Then the organic solvent was slowly evaporated under reduced pressure to form drug particles precipitating in the aqueous phase forming the aqueous suspension of the drug in the required particle size. Thesuspension formed can be suitably diluted to get nanosuspensions. Moreover, microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension. [20].

- **Emulsification-Solvent Evaporation Technique:**

This technique involves preparing a solution of drug followed by its emulsification in \another liquid that is a nonsolvent 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.

c) Applications of Nanosuspensions

- **Oral**

Oral drug delivery is the most widely preferred route of Administration of drugs. But, some drugs possess the Problem of limited bioavailability due to poor solubility And absorption which ultimately reduces its efficacy. In Such cases, Nanosuspension can solve the problem as it Helps in improving the dissolution rate and absorption Due to increased surface area and enhanced Adhesiveness. Nanosuspension can lead to increased Mucoadhesion which can increase gastrointestinal transit Time and lead to increased bioavailability. The Enhancement in oral bioavailability can be attributed to Increased surface area, saturation solubility and the Adhesiveness of the drug Nanosuspension. Taste masking Of particulate system is also easily possible.

- **Parenteral**

Nanosuspensions can be used to transform poorly soluble Non-injectable drugs into a formulation suitable for Intravenous administration. Although the production of Nanosuspension for parenteral use is critical, current Developments in this technology have proved its utility as injectable formulations. The methods used for preparation of Nanosuspension are now precisely controlled, and are able to produce uniform particles with better control over maximum particle size. Various research reports are available which emphasize the applicability of Nanosuspensions for parenteral administration.

- **Ocular delivery**

Nanosuspension can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions represent an ideal approach for ocular delivery of hydrophobic drugs due to their inherent ability to improve saturation solubility of drugs. Kassem et al., have developed Nanosuspension delivery system for certain glucocorticoid drugs

- **Pulmonary**

Nanosuspensions can be advantageous for delivering drugs that exhibit poor solubility in pulmonary secretion. Currently available approaches for pulmonary delivery such as aerosols or dry powder inhalers possess certain disadvantages such as limited diffusion at required site, less residence time etc, which can be overcome by Nanosuspensions. Fluticasone and budesonide have been successfully formulated as Nanosuspension for pulmonary Delivery.

- **Dermal**

The nanocrystalline form possesses increased saturation solubility resulting in enhanced diffusion of the drug into the skin. Nanocrystals also exhibit various properties such as increased penetration into a membrane, enhanced permeation and bioadhesiveness which could be very useful for dermal applications.

- **Pesticide Delivery**

In Pharmacology, development of a formulated nanosuspension, a potential drug delivery system for poorly soluble drugs, has been investigated to overcome the bioavailability problems caused by weak solubility, limited chemical stability following administration (i. e., a short half-life), poor bioavailability, and potentially strong side effects requiring drug enrichment at the site of action. For first time use in a pesticide delivery system, a two-step milling process for preparing a nanosuspension in a system

of active compound/surfactant/water is described in this paper. First, all the components were mixed at a certain composition to prepare a microsuspension by the general milling process. Then, the microsuspension was taken into a nanomilling process with zirconium oxide beads, having a diameter range of 0.1–0.2 mm, as the milling media to generate the nanosuspension. Therefore, a nanosuspension concentrate was formed. To demonstrate the potential applications of this novel system, it was used to make a formulation with a poorly soluble crystalline insecticide, carbofuran. In a comparative study, two kinds of carbofuran formulations, a microsuspension (commercial) and a nanosuspension, were administered to a diamondback moth (DBM) to test their efficacy and stability as a pesticide. The results indicate that carbofuran has the same efficacy at a lower dose for the nanosuspension compared to the microsuspension. The nanosuspension system was also physically and chemically stable over a period of 2 years, as indicated by the unchanged particle size and specification tests.

- **Electricity**

Suspensions with varying volume fraction of TiO2 nanoparticles and ionic strength were electrosprayed to obtain agglomerates of different characteristics, which were then deposited to produce films with tailored morphology, thickness, and porosity. The role of the nanoparticle volume fraction in both the effective electrical conductivity of TiO2 nanosuspensions and the control of the size of agglomerates produced by electrospray was investigated. A simple modified equation for the effective electrical conductivity of TiO2 nanoparticle suspensions was derived. The equation, which accounted for nanoparticles' diffuse ionic layer and their agglomeration in a liquid, showed that the effective electrical conductivity is not only a function of the liquid and particle conductivities, and the particle volume fraction but also a function of both the thickness of the adsorbed ionic layer on the particles and the particle size. Gradual increase of particle volume fraction resulted in an increase in the suspension's effective electrical conductivity, when the initial liquid conductivity was in the range of 104–103Sm1. When the liquid conductivity was in the range of 103–102Sm1; however, addition of particles did not have any significant effect on the effective electrical conductivity. Control over the size of the TiO2 nanoparticle agglomerates was achieved by electrospraying suspensions with liquid electrical conductivity of the order of 103Sm1 and by varying the particle volume fraction. Electrospray deposition of suspensions with TiO2 volume fraction=0.04% resulted in a more compact film with lower porosity and showed better water-splitting performance

Advantages of nanosuspension drug delivery system:-

1) Generally applicable to most drugs & simplicity.
2) Can be applied for poorly water-soluble drugs.
3) Can be given by any route.
4) Reduced tissue irritation in case of subcutaneous/ intramuscular administration.
5) Rapid dissolution & tissue targeting by IV route of administration.
6) Administration provides rapid onset, reduced fed/fasted ratio & improved bioavailability.

Disadvantages

1) Generation of residues of milling media, which may be introduced in the final product as a result of erosion.
2) The media milling technique is time consuming.
3) Some fractions of particles are in the micrometer range.
4) Scale up is not easy due to mill size and weight [21]

3. Results and Discussion

3.1 Considerations for Selection of Stabilizers

- Manufacturing of nanosuspensions involves the generation of a large number of small particles with enormous surface area. This significantly increases the Gibb's free energy of the system and, due to the high interfacial tension, these systems are thermodynamically unstable. Accordingly, nanoparticles will tend to minimize their total energy by undergoing agglomeration [22]
- The process of agglomeration depends on the activation energy, which is influenced by the addition of stabilizers to the system (such as, surfactants and polymers). These stabilizers reduce the interfacial tension between the particles and the dispersion medium and act as wetting agents. The second requirement is to provide a barrier between the drug particles to prevent agglomeration by electrostatic attraction (ionic surfactants) or steric stabilization (nonionic surfactants and polymers) [22]
- It is well known that an appropriate stabilizer is very important to control particle growth during the production of uniform nanoparticles. Many reports have shown that if preliminary particles can be arrested efficiently by appropriate stabilizers, the nanosuspensions system can be maintained for a longer time [23]
- The adsorption properties of stabilizers can be affected by the nature of stabilizer and drug surface, for example, molecular weight is an important factor for polymeric stabilizers. The chain length should be high enough, so that polymers chains have an optimum length to overcome the Van der Waals forces of attraction. Furthermore, another important factor is the size of the polymer [24].
- Electrolytes are present in the gastrointestinal tract and the contact of the nanocrystals with these electrolytes cannot be avoided. Electrostatic stabilization is reduced in its efficiency in an electrolyte containing environment. To compensate for this it is ideal to use steric stabilizers, which are less impaired in their effect by electrolytes [25].
- The adsorption layer of the stabilizer shifts the plain of shear, at which the zeta potential is measured, to a larger distance from the particle surface. Consequently the measured zeta potential is lower. In such cases zeta potentials of about 20 mV are still sufficient to fully stabilize the system [26]. Generally, absolute zeta potential value higher than 60 mV is considered of extreme stability, 30 mV means good stability, 20 mV shows acceptable short term stability and less than 5 mV will induce fast particle aggregation [25]. However, this rough guideline is only viable to pure electrostatic stabilization or in combination with low-molecular

weight surfactants [25]. In this study Zeta potential was not determined since all stabilizer used act by steric stabilization.

- Based on the above consideration various surfactants and polymers which exhibit steric stabilization characteristics were preferably used in this study such as Tween 20, Tween 80, HPMC, PVP K30, PVA, PEG 400, Na CMC, and β-cyclodextrin. The selected stabilizers were screened by trials in terms of their performance and particle sizes. It was found that nanosuspension prepared using drug to stabilizer ratio of 9 : 1 produced large particle size and rapid precipitation was noticed. Increasing the ratio of stabilizer in the nanosuspension to 9 : 3 (3 : 1) resulted in a dramatic reduction in particle size without precipitation of the formed nanosuspension. Following a further increase in stabilizer concentration, the particle size was not markedly reduced, which indicated that the drug particle surface was already sufficiently enveloped by the stabilizer molecules.
- In conclusion, a preliminary study revealed that drug to stabilizer ratio of 3 : 1 was of choice in terms of performance and particle size.

4. Future Prospects

- Nanosuspension technology is a unique and novel Approach to overcome drug problems such as poor Bioavailability that are related with the delivery of Hydrophobic drugs, including those that are poorly Soluble in aqueous as well as organic media. ProductionMethods like media milling and high-pressure Homogenization have been successfully employed for Large scale production of Nanosuspensions.
- Nanosuspension technology can be combined with Traditional dosage forms: tablets, capsules, pellets, and Can be used for parenteral products. To take advantage of Nanosuspension drug delivery, simple formation Technologies and variety applications, Nanosuspensions Will continue to be of interest as oral formulations and Non-oral administration develop in the future. In Consideration to data available Nanosuspensions can be Considered as renaissance in formulation technologies for Coming years.

5. Conclusion

Nanosuspension formulation have been largely Solved the solubility as well as dissolution problems to Improve drug absorption. It has therapeutic advantages, Such as simple method of preparation, less requirement of excipients, increased saturation solubility and Dissolution velocity of drug. Numbers of drug Candidates are identified in drug discovery programs, But most of them are fairly poorly soluble. This Challenges in pharma research to develop novel Approaches to achieve a high solubility, stability and Bioavailability of the drugs. Nanosuspension is Commercially possible approach to solve the poor Solubility as well as poor bioavailability problems of the Drugs. For large-scale production of nanosuspension Formulation, high-pressure homogenization technology Has been widely used. A nanosuspension formulation Solves the poor solubility problems, but also improves Drug efficacy.

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