A review on problems related with nanosuspensions with its solutions

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***Abstract*: Solubility of any formulation in pharmaceutical industry is the important factor which is related to and affect to drug effectiveness and drug bioavailability and its performance. As we know half of the new drugs entering in market are poor water soluble. So enhancing solubility of these drugs becomes difficult task. But since last decade nanotechnology had played important role in enhancement of solubility of poorly soluble drug. Nanosuspension has become promising technology to overcome problems related with solubility due to its advantages and ability to deal with solubility and target the delivery of drug. Although it has advantages but it seems to have some critical problem regarding its stability and bioavailability. This article covers all the problems related with physical stability and chemical stability and also the ones which come while choosing method of preparation along with its solutions.**

***Keywords*: Nanosuspsension, Physical stability, Top down technology, sedimentation**

INTRODUCTION

More than half of the new drug candidate entering in the development pipeline fails due to their water insolubility. So to solve the problems related to drug solubility, nanotechnology is used, such as Nanosuspension which represents an interesting and potentially very useful method to improve the bioavailability of water insoluble drugs [1]. Nanosuspensions are described as colloidal dispersion of drug particles. It can be defined as very finely colloid, biphasic dispersed drug particle in an aqueous vehicle which is stabilized by surfactants and polymer [2]. It has particle size in the range between 1-1000nm [1]. Due to increased surface area, drug particle have an enhanced dissolution and that's why nanosuspension becomes one of the most upcoming key research areas in the field of drug delivery [3].Due to this they have some advantages and they are following-

1. They can be used for targeted delivery of drugs to the specific site which minimizes toxicity.
2. They reduce the fluctuations in therapeutic range and hence improved bioavailability.
3. Improved drug dissolution
4. Improved stability of drugs against enzymatic degradation.
5. Reduced dosing frequency due to the effect of controlled and sustained release which improves patient compliance.
6. There are various routes administration are available like oral, nasal, pulmonary, intraocular, parenteral, and transdermal [4, 5].

Despite having advantages of nanosuspensions they also show drawbacks such as manufacturing complexity in which production process is very tedious and has critical process parameters which has to be taken care of, such as rate of precipitation and prevention of crystal growth. Sometimes there is risk of residual organic solvent [4]. And also the problems like nanaotoxicity, stability problems like sedimentation, aggregation; caking, crystal growth takes place. So many factors affect nanosupension formulation like the method of preparation we are using for preparation, excipient used in nanosuspensions and their effect on toxicity and more importantly problems arise during manufacturing and after its storage. Above all problems should be considered while formulation of nanosuspension.

Stability related issues-

There are some physical and chemical factors that play significant role in the instability of nanosuspension. Stability can be categorised as physical stability and chemical stability [4].

Physical stability: Stability of any pharmaceutical formulation can be defined as the ability of product in particular container or system to remain within its chemical, microbiological, physical, toxicological, protective and informational specifications. Hence physical stability of nanosuspension becomes an important since it is thermodynamically unstable system [6]. Physical stability can refer to any number of attributes ranging from appearance to colour to viscosity [7]. Physical stability means condition in which particles don't aggregate and in which they remain uniformly distributed throughout the dispersion.

General problems associated with physical stability are sedimentation, caking, agglomeration, crystal growth and change in crystalline state [4].

Aggregation- This is the main reason behind low stability of nanosuspension. Aggregation may occur during preparation process or the shelf time when nanosuspension are not stabilized by appropriate stabilizer [1]. Many of the physical properties of nanosuspensions depend on the state of aggregation. Aggregation can be called as hard bond between primary particles [8]. Unsuitable stabilizer results into agglomeration of smaller particles [1]. Agglomeration is the weak bond between primary particles [9]. This is caused by phenomenon of Ostwald ripening [1]. Ostwald ripening also called as disproportionation. It is the process of

disappearance of small particles by dissolution and deposition on larger particles [9]. Particles present in nanosuspension formulation have Brownian motion and hence they colloid with each other and stick together. Coalescence takes place due to attraction between particles and van der walls forces. This phenomenon can be called as aggregation [8]. Aggregation process occurs when attractive forces between particles overcome in nanosuspension [11]. For top down approaches aggregates occurred due to increased surface area due to thermodynamic effect and it reduces the efficiency of process. For suspension having coarse particles and Brownian motion is negligible then aggregation may take place due to particle collision by diffusion sedimentation or imposed motion with the velocity gradient. Also during storage it becomes important to limit or restrain the aggregation therefore suitable stabilizer should be used [1]. To overcome aggregation problem there should be use of proper stabilizer so that nanosuspension will be stable. Steric and ionic stabilizers are generally used. The amphiphilic polymer TGPS it prevent coalescence by repulsive entrapic force. Also HPMC could be able to prevent aggregation. Again copolymers which bear alkynyl or azido groups can be used to prevent aggregation by click chemistry mediated cross linking.

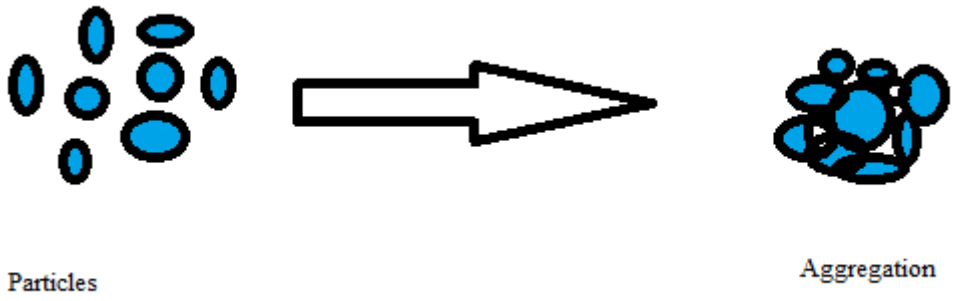

Fig. 1 Aggregation

Sedimentation –

Sedimentation is the property of nanosuspension which is governed by particle size, particle-particle interaction, medium and density of particle and also the viscosity of continuous phase [12]. Sedimentation is the presentation of instable phenomenon of the nanosuspension when there is gravity of the drug particle is greater than buoyancy force of dispersion system, sedimentation will take place. So to predict and prevent the sedimentation is the chief consideration in nanosuspension formulation as this process is irreversible and indispensible. Sedimentation takes place in both flocculated and deflocculated suspension but they differ in nature of sediment and rate of sedimentation [1]. In flocculated nanosuspension, rate of sediment is high while in deflocculated nanosuspension rate of sediment is low. Again sediment volume is high in flocculated suspension and in deflocculated suspension there is low volume of sediment [4].

Stokes law is formula used to determine the rate of sedimentation. It states that a particle moving through viscous liquid attain a constant velocity or sedimentation rate. The rate can be very slow for particle whose density is very close to that of liquid for particles whose diameter is small, or where the viscosity is high. The following is the equation for stokes law of sedimentation.

$Vg = d2 (Þp - Þ1) / 18\mu \times G$

Where:

Vg = sedimentation velocity

d = particle diameter

Þp = particle density

Þ1 = liquid density

G = gravitational acceleration

μ = viscosity of liquid

Fundamental properties such as mean sedimentation velocity, sedimentation microstructure are difficult to determine [4]. To resolve the sedimentation issue most of the time nanosuspension converted to drug solid powder by using spray dryer or freeze dryer. Freeze drying is not suitable for oily nanosuspensions.

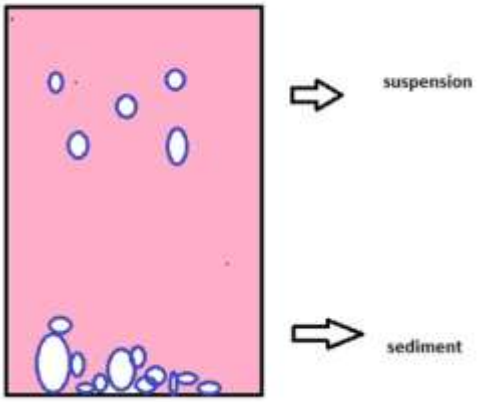

Fig. 2 Sedimentation

Caking- It is defined as the formation of nanodispersible sediment within a suspension system. Two reasons why caking takes place are crystal bridging and closed aggregate or coagulate formation. In crystal bridging, crystal growth of particle surface occurs and results into steady formation of crystal linked particles. Small change in temperature during storage period may lead to unexpected rapid caking through crystal bridging. Caking may also occur by extensive closed aggregate formation. To overcome with the caking problem especially caused by crystal bridging we can utilize the floccule suspension type which is open network aggregate. Because of rigidity of aggregates particles cannot sediment to close proximity. Fully aggregated suspension is often partial aggregation and leads to resistance to caking. By controlling the particle size distribution we can prevent caking [12].

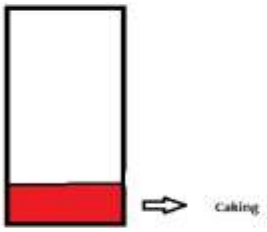

Fig. 3 Caking

Crystal growth- It is more common problem associated with colloidal suspension and responsible for particle size change and their distribution. This process happens to occur because of unequal solubility profile off particle depending on their size. In this process small particle attain a lower energy state after transform into large particle. This leads to unsaturated solution to surround the small particles. Surfactants play major role in inhibiting Ostwald ripening which causes crystal growth using proper surfactants and its concentration in the formulations can stabilize nanosuspension. It was reported that 0.2% PVA stabilizer nanosuspension for more than 6 months also using TGPS as stabilizer as showed the result. Also lowering the temperature 4^{o}C also stopped Ostwald ripening [4].

Changes in crystalline state

This is another stability issue related to nanosuspension. It also affects solubility, dissolution and drug's efficacy directly or indirectly. This is related with shear induced API form conversion of amorphous drug formation. Other than shear force some other factor are responsible for transformation like dispersion media, stabilizer and temperature. This type of problem can be solved by controlling the above factors and some modifications in manufacturing processes require like reducing the temperature we can use jacketed mill. And also by controlling the speed of rotation of mill we can control the problem [4].

Chemical stability – chemical stability is also an important factor that affects formulation of nanosuspension. Generally nanosuspensions are prepared in dispersion medium of water or water mixture environment although there were few processes operated in non-aqueous mediums. Therefore chemical stability problems such as hydrolysis and oxidation are a considerable issue in the formulation of nanosuspensions.

There are many factors which can lead to the chemical instability of nanosuspension like storage conditions like temperature and pH, chemical stability of drug entrapped and also the type of polymer and its molecular weight that play a vital role in chemical instability of nanosuspensions. Polymer degradation may takes place due to extreme conditions of PH and temperature. Overall stability of formulation also depends on chemical stability of drug entrapped. Drugs show pH. Dependant degradation and under certain conditions they show photo degradation profile [1]. Solutions to chemical instability are adjusting the pH to physiological pH because it gives best stability. If you are using biodegradable polymer in formulation then formulation should be stored at 4-50˚c temperature for better results [4]. Best way to solve the problem is to convert the nanosuspension to dry and solid form [20].

Challenges while choosing method of preparation

There are two converse methods for manufacturing of nanosuspension which are bottom up technology and top down technology [13]. The conventional method bottom up process which is related to precipitation in which drug is dissolved in a solvent and then it added to non-solvent to precipitate the crystals [14]. Bottom up process includes

- Solvent- anti solvent method
- Supercritical fluid process
- Emulsification solvent evaporation method
- Liquid emulsion / micro-emulsion template [12].

Top down technologies mainly involves disintegration methods which are preferred over precipitation methods. This technology includes the following processes

- Media milling- nanocrystals
- High pressure homogenization
  - In water- dissocubes
  - In non-aqueous media- nanopure
- Nanoedge – combination of precipitation and high pressure homogenization.

As we go for bottom up process, we need to consider the following disadvantages of this process.

- In this method drug needs to be soluble in at least one solvent. Also the solvent must be miscible with at least one non solvent.
- You need to do second consecutive process such as spray drying or lyophilisation for particle presentation as it is little bit difficult to present the particle character [5].

Top down processes has some of the following limitations-

- We cannot use harsh solvent in this process
- This process involve high energy input and which is inefficient
- Formulation of thermolabile material becomes difficult as it generates considerable amount of energy [15].

Media milling-

- The major problem in this process is that it involves erosion of balls or pearls that may leave residues as contaminants in the final product also degradation of thermolabile drugs.
- Duration of process in not very production friendly [5]
- It is slow process and unstable [16]
- It cannot be used for both diluted as well as concentrated suspensions [17]

High pressure homogenization-

- This process is useful and commonly used but it has some drawbacks like you need to maintain strict temperature control and also premicronization of suspension to prevent any type of blockage during homogenization [18].
- This process consumes high energy
- It requires experience in operation [16]

Nanojet technology-

Major drawback of this technology is high number of passes takes place through microfluidizer and that's why product contains large fraction of micro particle [17].

Solvent antisolvent method-

This process cannot be used for drugs which are poorly soluble in aqueous and non-aqueous media. The major challenge is to avoid crystal growth [19].

Emulsion diffusion method-

- Due to usage of hazardous solvent, safety is concerned.
- Process becomes so costly because there is need for ultrafiltration for purification of drug.
- Major amount of stabilizers or surfactants is needed for production [5].

Supercritical fluid method-

Due to high saturation there may be particle nucleation growth which results into development of undesired polymorph [5].

Solutions for choosing method of preparation while formulation

For the process of precipitation, problem like crystal growth occurs so choose the nanoedge technology for formulation because it can solve the problem of crystal growth. Melt emulsification process produces larger particles so prefer solvent evaporation for better results. In processes like emulsion diffusion and microemulsion template instead of hazardous solvents like dichloromethane or chloroform use some less hazardous water miscible solvent like methanol; ethanol or isopropanol can be used. And also partially water miscible solvents like ethyl acetate and ethyl formate or benzyl alcohol can be used [13]. As media milling cannot be used for both dilute and concentrated suspensions so there should be use of high pressure homogenization technique for both types of formulations. Wet milling and high pressure homogenization technique is not suitable for thermolabile substances so nanopure technology can be used instead those techniques as it gives better results for thermolabile substances [21].

Conclusion -

Stability of any formulation is crucial factor, because it is related to efficiency and performance of pharmaceutical formulation. Nowadays issues related with stability can be solved by using nanosuspensions. This strategy has become very useful for enhancing solubility of drug as well as dissolution and bioavailability of poor water soluble drug. There are also other factors other than stability which affects efficiency of formulation like nature of drug and excipients, routes of administration, method of preparation, interaction between drug and stabilizers.

There are still some problems that are difficult to overcome which are choosing suitable stabilizer, understanding the mechanism of interaction between drug particles and stabilizer. Also there is need to focus on approaches for new preparation techniques. Currently self-stabilized nanosuspensions are highly demanding but very little research work has been done on it so it can be future aspect for research in nanosuspension.

Acknowledgement:

The authors are thankful to Principal, Government College of Pharmacy, Karad.

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