Nano suspension Approach for Drug Delivery System: A Review

Priyeshnath Rathod
Assistant Professor
Department of Chemical Engineering
Parul Institute of Technology
Parul University, Vadodara, India.

Abstract: Nanotechnology has brought about a tremendous change in the field of medicine and pharmacy and still continues to do so. Nanosuspensions a form of this technology has proved its worth in the field of medicines. Drugs that were poorly soluble in aqueous as well as inorganic media were made available by use of nanosuspension technology. Transfer of materials into the nanodimension changes their physical properties which were used in pharmaceutics to develop a new innovative formulation principle for poorly soluble drugs: the drug nanocrystals. The drug nanocrystals do not belong to the future; the first products are already on the market. Nanosuspensions are prepared using various techniques like high pressure homogenization, media milling, solvent precipitation, etc. Lots of studies have been undertaken in developing method which is economical and can be expanded industrially. This is because drugs are usually expensive. There are advantages and disadvantages to all the methods available for preparing nanosuspensions. Usually high pressure homogenizer is preferred for preparing nanosuspensions as it can be industrially scaled up. Choice of polymeric surfactants for stabilizing nanosuspensions has been studied less. Storage stabilities of nanosuspensions have been determined using parameters like particle size and particle charge.

Keywords - Nanosuspenstion, Rheological Properties, Nanocrystals, Bioavailability & Solubility Enhancement, Homogenization

I. INTRODUCTION

A Nanosuspension is defined as "very finely dispersed solid drug particles in an aqueous vehicle, stabilized by surfactants, for either oral or topical use or parentral and pulmonary administration, with reduced particle size (10-1000nm),leading to an increased dissolution rate and therefore improved bioavailability [1].

In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability [2]. Nano sized particles can increase solution velocity saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient result to a much more pronounced increase in the dissolution velocity as compared to a micronized product. These particles are stabilized by polymers and surfactants prepared by suitable methods for delivery by mean of various route of administration like topical, parenteral, oral [3].

More than 40% of drugs are poorly soluble in water, so they show problems in formulating them in conventional dosage forms. Also, for class II drugs which are poorly soluble in aqueous and organic media, the problem is more complex. In above cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in inorganic media instead of using lipidsystems, nanosuspensions are used as a formulation approach [4].

II. PREPARATION OF NANOSUSPENSION

Nanosuspensions can be made by 'bottom up technology' and 'top down technology'. Drug nanocrystals produced by bottom up technology use precipitation approach. The mechanism is to dissolve drug in a solvent which is subsequently added to a nonsolvent to precipitate the crystals. The three basic technologies currently in use and owned by different companies are: (i) Pearl milling (nanocrystals) (ii) Homogenisation in water (Dissocubes) (iii) Homogenization in nonaqueous media or in water with water miscible liquids (Nanopure); The precipitation technique is not for those drugs that are poorly soluble in aqueous & non-aqueous media. The major challenge in this technique is prevention of Ostwald ripening which manifests as crystal growth [5][6][7].

The nano precipitation technique or solvent displacement method was first developed and patented by Fessi and co-workers in 1988. This technique is straight forward and easy to perform. Nanoparticle formation takes place in one step instantaneously. This is governed by Marangoni effect, which is due to interfacial turbulences taking place at the interface of the solvent and non-solvent [8] [9].

METHODS OF PREPARATION:

[A] BOTTOM UP TECHNOLOGY:

The conventional methods of precipitation (Hydrosols) are called Bottom Up technology. [9] Using a precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible antisolvent. In the water-solvent mixture the solubility is low and the drug precipitates. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent[10].

[B] TOP DOWN TECHNOLOGY:

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 High Pressure Homogenization in nonaqueous media (Nanopure), Precipitation, High-Pressure Homogenization[11].

Media milling (Nano Crystals): This patent-protected technology was developed by Liversidge et al (1992). Formerly,the technology was owned by the company NanoSystems but recently it has been acquired by Elan Drug Delivery. In this method the nanosuspensions are produced using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the micro particulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked polystyrene resin[11][12][13].

High pressure homogenization: R.H.Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 –1500 bars (2800–21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale).High pressure homogenization has been used to prepare nano suspension of many poorly water soluble drugs. In the high Pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer[14][15]. The particles cavitations forces are sufficiently high to convert the drug micro particles into nano particles.

***Nanojet technology*:** In this technique the precipitated suspension is further homogenized to get smaller particle size and to avoid crystal growth is performed in water using water miscible solvent, as methanol, ethanol, and isopropanol. It is desired to remove the solvent completely by including evaporation step to provide a solvent free modified starting material followed by high pressure homogenization.

An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion18.The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion.

Supercritical fluid method: The organic solvents used in the preparation of conventional methods as solvent extraction evaporation, solvent diffusion and organic phase separation methods are hazardous to environment and physiological systems. To rectify the problem occurred through the conventional method supercritical fluid technology has been investigated for the preparation of biodegradable micro and nanoparticles, because supercritical fluids are environmentally safe. The most common techniques using supercritical fluids are supercritical anti-solvent (SAS), precipitation with compressed anti-solvent process (PCS) and rapid expansion of supercritical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (SC CO2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles.

III. FORMULATION OF NANOSUSPENSION

Stabilizer: The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. The high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent Ostwald's ripening (Rawlins 1982; Mu¨ ller & Bo¨hm 1998) and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers.

Organic solvent: The pharmaceutical acceptance & less suitable hazardous water miscible solvents, such as ethanol & isopropanol and partially water miscible solvents, such as ethyl acetate, ethlyl formate,butyl lactate, triacetin, propylene carbonate & benzyl alcohol are preferred in the formulation of nanosuspensions.

Co-surfactant: The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated[17]. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsionsThe pharmaceutical acceptance & less suitable hazardous water miscible solvents, such as ethanol & isopropanol and partially water miscible solvents, such as ethyl acetate, ethlyl formate,butyl lactate, triacetin, propylene carbonate & benzyl alcohol are preferred in the formulation of nanosuspensions.

Additives: Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety. -Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiet.

IV. CHARCTERIZATIONS OF NANOSUSPENSION

Mean Particle size and Particle size distribution: The mean particle size and the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of nanosuspension. It has been indicated by Muller & Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug.

Crystalline state and particle morphology: The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nano sizing. Additionally, when nano suspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug nano particles generated during the production of nano suspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and can be supplemented by differential scanning calorimeter. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred.

Particle Charge (Zeta potential): The determination of the zeta potential of a nano suspension is essential as it gives an idea about the physical stability of the nano suspension. The zeta potential of a nano suspension is governed by both the stabilizer and the drug itself. In order to obtain a nano suspension exhibiting good stability, for an electrostatically stabilized nano suspension a minimum zeta potential of -30mV is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of -20mV is desirable.

X-Ray Diffraction: The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug. It is important to know the crystal morphology of the drug in the nanosuspension. Polymorphic or morphological changes in drug that occur during nano-sizing can be determined by the knowledge of crystalline state and particle morphology. Amorphous state of the drug formed during preparation of nanosuspension is determined by X-ray diffraction analysis. It gives information about the changes in the physical state of the drug particles as well as the extent of the amorphous fraction.

In vitro & In vivo Evaluation: The particle size, particle size distribution, and zeta potential affect the safety, efficacy, and stability of nano drug delivery systems as well as dissolution performance is also altered by solid state of nano particles. Thus, characterization of nano particles plays a great role in forecasting *in vitro* and *in vivo* performance of nano drug delivery systems. *In vivo* pharmacokinetic performance and biological function of nanosuspension strongly depends on its particle size and distribution, particle charge (zeta potential), crystalline state, and particle morphology. The establishment of an in-vitro/in-vivo correlation and the monitoring of the in-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed.

Swelling Study: The differences at early time points were observed due to difference in the swelling properties of the gel forming polymers which impacted the lag time. The amorphous polymer film swelling in a liquid solvent below the glass transition temperature was characterized by a few kinetic parameters (especially the mutual diffusion coefficient of swelling and its mean value) obtained by interference of monochromatic light in the wedge arrangement.

Drug content: Drug content of nanosuspension formulation was carried out by mixture of polymer and drug, mixture was centrifuged by 1000 to 4000 rpm. The drug content was calculated by the calibration curve from absorbance with time by using UV spectrometer.

V. APPLICATION OF NANOSUSPENSTION

Oral Drug Delivery: The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the GIT. Nano-sizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability and increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body.

Topical Formulation: Drug nano particles can also be incorporated into water free ointments and creams, which have an increased saturation solubility and enhanced diffusion of drug into the skin. The nano crystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug.

Pulmonary Drug Delivery: The drug nanosuspension can using commercially available nebulizers. Disposition in the lungs can be controlled via the size distribution of the generated aerosol droplets. Drug nano crystals show increased much adhesiveness, leading to a prolonged residence time at the mucosal surface of the lung [35]. Hernandez-Trejo and coworkers formulate physically stable nanosuspensions were formulated to deliver bupravaquone at the site of lung infection using nebulisation.

Target Drug Delivery: The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems.Nanosuspensions affords a means of administrating poorly soluble drugs to brain with decreased side effects. Surface modified polyisobutyl cyanoacrylate nanoparticles.

Formation of nano particle: When nano particles are administered orally in the form of a suspension, they diffuse into the liquid media and rapidly encounter the mucosal surface. They adhere to the intestinalnsurface (bioadhesion) and get immobilized. After

adhesion, the concentrated suspension acts as a reservoir of particles and enables the rapid adsorption. The first step before particle absorption is the direct contact of the particles with the intestinal cells through a bioadhesive phase.

VI. CONCLUSION AND FUTURE ASPECTS

The literature review of nanosuspensions, give us the idea about the extent to which it is being used in making drugs bioavailable. Nanosuspension technology has become a boon in the health sector. By combining it with the traditional dosage forms, it has solved problems in various drug delivery paths. If the gap between the in-vitro and in-vivo can be completed, the future of the hydrophobic drugs can become absolutely clear.

VII. REFERENCES

1. Dhanapal R, Ratna JV. Nanosuspensions technology in drug delivery – a review. Int J Pharm Rev Res 2012;2: 46-52
2. Mohanraj VJ, Chen Y. Nanoparticles – A Review. *Trop J Pharm Res* 2006; 5(1): 561- 573
3. Krishna K B, Prabhakar C. A review on nanosuspensions in drug delivery. Int J Pharma Bio sciences 2011;2: 549– 58
4. Bushrab FN, Müller RH. Nanocrystals of Poorly Soluble Drugs for Oral. Journal of Pharmacy and Pharmacology 2002;30: 426–39
5. Das S. Nanosuspension: An Assuring Novel Drug Delivery System. Int J Pharm Sci Rev Res 2013; 20(1):228-31
6. Lakshmi P, Kumar GA. Nano-suspension Technology: A Review. Int J of Pharm Pharm Sci 2010; 2(4): 35-40
7. Sahu BP, Das MK. Nanosuspension for enhancement of oral bioavailability of felodipine. Appl Nanosci 2014; 4: 189-97
8. Malakar J,Basu A, Ghosh A.Nanosuspension:A Nano-Heterogeneous Carrier for Drug Delivery System. International Journal of Pharmaceutical and Biological Archives 2012; 3(1):4-13
9. Shid RL, Dhole SN, N Khulkarni, Shid SL. Nanosuspensions: A Review. Int J Pharm Sci Rev Res 2013; 22(1): 98-106B.
10. Kavitha VB, Neethu CS, Dineshkumar B, Krishnakumar K, John A. Nanosuspension Formulation: An Improved drug delivery system. Nanoscience and Nanotechnology: An International Journal. 2014; 4(1): 1-5
11. Venkatesh T, Reddy AK, Maheswari JU, Dalith MD, Ashokkumar CK. Nanosuspensions: Ideal approach for the drug delivery of poorly water soluble drugs. Der Pharmacia Lettre 2011;3(2): 203-13
12. Wu ZM, Zhou L,Guo XD,Jiang W,Ling L,Qian Y,Luo KQ, Zhang LJ. HP55-coated capsule containing PLGA/RS nanoparticles for oral delivery of insulin.International Journal of Pharmaceutics 2012; 425:1-8J.
13. Keck CM, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization. European Journal of Pharmaceutics and Biopharmaceutics 2006; 62(1): 3-16
14. Patel M , Shah A, Patel NM, Patel MR, Patel KR. Nanosuspension :a novel approach for drug delivery system. Journal of pharmaceutical science and bioscientific research 2011;1(1):1-10
15. Steffi PF and srinivasan M. preparation, characterization and stabilization of curcumin nanosuspension, International Journal of PharmTech Research 2014;6(2):842-849
16. Mishra S, Panda DB, Pradhan M, Hussain I. Preparation and evaluation of ezetimibe nanosuspension. Journal of advanced pharmaceutical research 2011; 2(4):185-189.
17. Satyajit CVN, Rao MEB, Patro CN, Swain S, Taria S, Kumar S. Formulation, characterization, and in vitro evaluation for solubility enhancement of a poorly water soluble drug using nanoedge technique. World Journal of Pharmaceutical Research 2014; 3(4):2152-2167
18. Shinde NC, Keskar NJ, Argade PD. Nanoparticle: Advances in drug delivery systems research journal of pharmaceutical, biological and chemical sciences 2012; 3(1): 922-929.
19. Lee S, Bairstow SF, Werling JO, Chaubal MV, Lin L, Murphy MA, DiOrio JP, Gass J, Rabinow B, Wang X, Zhang Y, Yang Z, Hoffman RM. paclitaxel nanosuspension for targeted chemotherapy. Pharm Dev Technol 2014;19(4): -53
20. Ahuja BK, Jena SK, Paidi SK, Bagri S, Suresh S. Formulation, optimization and in vitro– in vivo evaluation of febuxostat nanosuspension. International Journal of Pharmaceutics 478 (2015): 540–552
21. Salazar J, Müller RH, and Möschwitzer JP. Combinative Particle Size Reduction Technologies forthe Production of Drug Nanocrystals. Journal of Pharmaceutics, 2014: 1- 14
22. Aditya NP, Yang H, Kim S, Ko S. Fabrication of amorphous curcumin nanosuspensions using β-lactoglobulin to enhance solubility, stability, and bioavailability. Colloids and Surfaces B: Biointerfaces 127 (2015): 114-121
23. Yang X, Miao X, Cao F, Li S, Ai N, Chang Q, Lee SMY, Zheng Y. Nanosuspension development of scutellarein as an active and rapid orally absorbed precursor of its BCS Class IV Glycoside Scutellarin. Journal Of Pharmaceutical Sciences 103 (2014): 3576- 3584
24. Liu Y, Kathan K, Saad W, and Prud'homme RK. Ostwald ripening of β-carotene particles. Physical Review Letters 98 (2007): 1-4
25. Hend M. Shubar HM, Lachenmaier S, Heimesaat MM, Lohman U, Mauludin R, Muller RH, Fitzner R, Borner K, and Liesenfeld O. SDS-coated atovaquone nanosuspensions show improved therapeutic efficacy against experimental acquired and reactivated toxoplasmosis by improving passage of gastrointestinal and blood–brain barriers. Journal of Drug Targeting 2011; 19(2): 114–124
26. Krause KP, Muller RH. Production and characterisation of highly concentrated nanosuspensions by high pressure homogenisation. International Journal of Pharmaceutics 214 (2001): 21-24
27. Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. International Journal of Pharmaceutics 312 (2006): 179-186
28. Muller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy Rationale for development and what we can expect for the future. Advanced Drug Delivery Reviews 47 (2001): 3-19
29. Zhu X, Mason TG. Nanoparticle size distributions measured by optical adaptive- deconvolution passivated-gel electrophoresis. Journal of Colloid and Interface Science 435 (2014): 67-74
30. Donoso MD, Haskell RJ, Schartman RR. Surfactant choice and the physical stability of nanosuspensions as afunction of pH. International Journal of Pharmaceutics 439 (2012): 1-7