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Nanosuspension Technologies : A Innovative Approach in Drug Delivery of Sparingly Soluble Drugs

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ABSTRACT

Nanotechnology is the science that deals with the process that occurs at molecular level and of nano length scale size. Nano refers to the particle size range of 1-1000 nm. Nanosuspensions are coming under nanotechnology. A pharmaceutical Nanosuspension is defined as very finely colloid, biphasic, dispersed solid drug particles in an aqueous vehicle, size below 1μm stabilized by surfactants and polymers prepared by suitable methods for drug delivery applications. It provides efficient delivery of hydrophobic drugs and increases the bioavailability. Nanosuspension is an attractive and promising technology to improve poor solubility and bioavailability of the drugs. This review article describes the methods of preparation, and applications of nanosuspensions in the field of pharmaceuticalsciences.

Keywords: Nanotechnology, Nanosuspensions, polymers,drugs.

INTRODUCTION

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 reas such asdiagnostics,therapeutics and prognosis. The main advantage of particles in the nano-metric range is its improved physical and chemical properties.The major parameters in drug delivery include particle size, surface area, hydrophobicity, crystallinity and surface charge. More than 40% of new chemical entities being generated through drug discovery programmesare poorly water soluble. The formulation of poorlywatersoluble drugs has always beena methodssuch as micronization, solubilisation using co-solvents, surfactant dispersions and precipitation technique has been developed for improving solubility of poorly watersoluble drugs. But these techniques show limitations to the drugs which are not soluble in both aqueous and organic solvents. Nanosuspension technology can be used to solve the problems associated with various approaches described earlier. Nanosuspension is colloidal dispersion of nano-sized drug particles stabilized by surfactants. They can also define as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle. The diameter of suspended particle is less than 1µm in size.

When to go for Nano Suspensions Approach

- Preparing nano suspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value.
- Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic
- In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems Nanosuspensions are used as a formulation approach.
- Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.24,25
- According to Noyes–Whitney equation, drugs with smaller particle size have enlarged surface areas which lead to increase dissolution velocity. Higher the dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation could further increase oral bioavailability of drugs. A nanosuspension is a submicron colloidal dispersion of drug particles which are stabilized by surfactants

- A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for oral, topical, parenteralorpulmonaryadministration.Theparticle sizedistributionofthesolidparticlesinnanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. In nanosuspension technology, the drug is maintained in the required crystalline state with reducedparticle size, eading to an increased dissolution rate and therefore improved bioavailability

CRITERIA FOR SELECTION OF DRUG FOR NANOSUSPENSIONS

Nanosuspension can be prepared for the API that is having either of the followingcharacteristics

- Water insoluble but which are soluble in oil (high logP) or API are insoluble in both water andoils.
- Drugs with reduced tendency of the crystal to dissolve, regardless of the solvent.
- API with very large doe.

ADVANTAGES OF NANOSUSPENSION DRUG DELIVERY SYSTEM

- It can be applied for poorly watersoluble drugs.
- Physically more stable thanliposomes.
- Most costeffective.
- Reduction in tissueirritation.
- Improved dose proportionality

FORMULATION OF NANOSUSPENSION

- **Stabilizers:**

  Wet the drug particles thoroughly; prevent Ostwald's ripening and agglomeration of nanosuspensions, providing steric or ionic barriers. Eg: Lecithins, Poloxamers, Polysorbate, Cellulosics, Povidones.

- **Cosurfactants:**

Influence phase behavior when micro emulsions are used to formulate nanosuspensions. e.g.: Bile salts, DipotassiumGlycerrhizinate, Transcutol, Glycofurol, Ethanol, Isopropanol.

- **Organic solvent:**

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.

- **Other additives:**

According to the requirement of the route of administration or the properties of the drug moiety. e.g.: Buffers, Salts, Polyols, Osmogens, Cryoprotectan.

TECHNIQUES OF PREPARATION OF NANOSUSPENSION

Media Milling:

The media milling technique was developed by Liversidge et al. In this method high-shear media mills or pearl mills are used to produce nanosuspension. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber. The milling media or balls are framed in ceramic-sintered aluminium oxide or highly cross-linked polystyrene resin. The milling chamber is fed with an aqueous suspension of the drug, stabilizer, and the milling media or pearls rotate at a very high shear rate.This procedure can be carried out under controlled temperature.The friction and collisions among drug particles and pearls generate nanoparticles. Ease of scale-up and little batch-to-batch variation are the advantages of media milling. Disadvantage of this method is the erosion of pearls which leads to contamination of the final product and subsequently problems upon administration.

High Pressure Homogenization:

High pressure homogenization is a commonly employed method for producing nanosuspensions of poorly soluble drugs. This method involves forcing a suspension, which contains drug and stabilisers, through a valve with a small orifice under pressure. High pressure homogenization is often classified into two groups:

a) Dissocubes (homogenization in aqueous media)
b) Nanopure (homogenization in water-free media or water mixtures).

Dissocubes operates at high pressure of up to 1500 bar where a suspension passes through asmallgap.This causes an increase in the dynamic pressure with simultaneous reduction in the static pressure which reduces the boiling point of water to room temperature. Consequently, at room

temperature water starts boiling creating gas bubbles. When the suspension departs the gap and the pressure returns to atmospheric level, the gas bubbles implode. This phenomenon is called cavitation. The combined forces of cavitation, high shear, and collisions lead to fracture of the drug microparticles into nanosized particles. Homogenization pressure, number of homogenization cycles, hardness of drugs, and temperature (when thermosensitive drugs are processed) are factors that influence the physical characteristics (such as particle size) of the resulting nanosuspensions. Metal contamination due to the erosion is less pronounced in this technique than in media milling. High pressure homogenization is considered as a safe technique for producing nanosuspensions. Less than 1 ppm metal contaminations were detected under processing condition of 20 cycles and pressure of 1500 bar. The main drawback of this method is the need for pretreatment to obtain microparticles before starting the homogenization process and the many cycles of homogenization. For some purposes such as dispersing drug nanocrystals in low molecular weight PEG or in oil, liquid nanosuspensions are dispersed in nonaqueous media or media with reduced water content. Because of the high boiling point and low vapour pressure of oily fatty acids and oils, the drop in pressure is not sufficient for cavitation and thus the latter is not a determining factor in this process. To compensate for insufficient drop in pressure, the Nanopure process is conducted at low temperature which is often referred to as "deep-freeze" method. Conducting the process at 0∘ C or even below the freezing point produces results comparable to those achieved using dissocubes.

Microprecipitation:

High Pressure Homogenization (Nanoedge Technology). Nanoedge Technology was developed by Muller. The technology consists of two processesprecipitation of drug particles and their fragmentation by using high pressure homogenization. Generally, this technique includes mixing of two different solutions. The drug is dissolved in an organic solvent which is miscible with water and forms the organic phase. The stabilisers are dissolved in the aqueous phase in which the drug is insoluble. Mixing these two solutions causes precipitation of drug particles. The last step of the process is high pressure homogenization.

Emulsion Diffusion Method:

This method uses partially water-miscible and volatile organic solvent such as butyl lactate, benzyl alcohol, triacetin, and ethyl acetate as the dispersed phase. The emulsion is prepared by dispersing the drug loaded in a mixture of solvents or an organic solvent and forming emulsion with water by high pressure homogenization or other techniques. Dilution leads to formation of nanosuspensions by

diffusion of the internal phase into the external phase when droplets convert into solid particles. The size of the emulsion droplets determines the particle size. The use of organic solvents such as ethyl acetate, ethanol, methanol, and chloroform and the presence of residual solvents in the final products are major drawbacks of this technology due to potential environmental hazards and human safety issues. Acyclovir nanosuspensions have been produced by emulsion diffusion method.

Melt Emulsification Method:

Melt emulsification method has been used to prepare solid lipid nanoparticles. Kocbek. are the first authors to use the melt emulsification technique to prepare 100 nm ibuprofen nanosuspensions with traditional excipients such as Tween 80 and polyvinylpyrrolidone. The first step in melt emulsification involves dispersing the drug in aqueous solution with stabilizer. Secondly, the nanosuspension is heated above the melting point of the drug and homogenized with a high-speed homogenizer to produce an emulsion. During this procedure the temperature must be controlled and maintained above the melting point of the drug. The final step of the melt emulsification method is cooling off the emulsion to a suitable temperature, either at room temperature or in an ice bath. Factors affecting particle size include drug and stabiliser concentrations, type of stabiliser, and cooling condition. Solvent free prepared nanosuspensions are particularly important from toxicity point of view. Therefore, the advantage of this method over solvent diffusion method is avoidance of organic solvents. Ibuprofen nanosuspensions prepared by this technique have been reported to increase the dissolution rate to over 65% after 10 min compared to just 15% for micronized ibuprofen dissolved after the same period.

Nanosuspension Characterization

Size:

The most important characteristics of nanosuspensions are particle size and polydispersity index (PI: particle size distribution).Particlessize of nanosuspensions critically determines the following characteristics of nanosuspensions

i) drug saturation solubility

ii) physical stability

iii) dissolution rate

iv) bioavailability

Crystalline State and Particle Morphology.

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

Particle Charge (Zeta Potential)

Particle charge plays an important role in ensuring stable nanosuspensions. The electric charge on a particle surface provides electrostatic repulsion between the drug nanoparticles and in this way prevents particles from aggregation and precipitation. The schematic in Figure 3 provides an illustration of the electric double layer around a charged particle. The double layer consists of a stern layer and a diffusion layer of opposite ions. The electric potential at the shear plane is known as the zeta potential. It is considered that a minimum zeta potential of ±30 mV is required to ensure pure electrostatic stabilization. When electrostatic stabilization is combined with steric stabilization (by using appropriate polymers), zeta potential of ±20 mV could be sufficient to prevent drug particles from aggregation and precipitation. Steric stabilization is defined as stabilization caused by the adsorbed and hydrated polymer layers on the dispersedparticle.Particlescharge is typically determined by measuring electrophoretic mobility upon application of an electric field which is then converted to zeta potential by using the Helmholtz-Smoluchowski equation. The zeta potential can also be measured by applying an ultrasound wave which induces the so-called electroacoustic phenomena

Stability

Reduction in particle size results in increased surface energy due to the greater number of unstable surface atoms and molecules. This destabilises the colloidal suspension. Therefore, the use of stabilisers is often necessary to avoid particle agglomeration and reduce the possibility for Ostwald ripening. Common stabilisers used to formulate nanosuspensions include polysorbates, povidones, poloxamer, lecithin, polyoleate, and cellulose polymers. Mixture of surfactants and polymers has been found to be beneficial for long-term stabilization of nanosuspensions. Polymeric materials and surfactants act as an ionic barrier and/or inhibitors of the close interaction between particles. Surfactants can increase the electrostatic repulsion and improve particle stability by altering the zeta potential. Precipitation of particles is another phenomenon that should be taken into account when considering stability of nanosuspensions. According to Stoke's law, decreasing particle size, reducing the density difference of solid phase, and increasing the viscosity of the medium decrease the precipitation velocity

$$\mathbf{V} = \frac{2r2\,(\rho 1 - \rho 2)\,g}{(9\eta)}$$

where V is the precipitation velocity, r is the particle size, $\rho 1$ is the mass density of particles, $\rho 2$ is the mass density of fluid, g is the gravitational acceleration, and η is the viscosity of the medium. The stability of nanosuspension system can also be increased by increasing the uniformity of particle sizes by using centrifugation or other techniques to remove larger particles.

APPLICATIONS OF NANOSUSPENSION:

Oral Drug Delivery

Because of the numerous advantages oral route is the most preferable route for many of the drugs especially in the case of orally administering antibiotics such as atovaquone and bupravaquone. By making it in nanosize, its solubility and bioavailability will increase. The oral administration of naproxen nanoparticles leads to an area under the curve (AUC) (0-24 h) of 97.5 mgh/l compared with naproxen nanosuspension and naproxen tablets. In the case of danazole (gonadotrophin inhibitor) nanosuspension has absolute bioavailability of 82.3 and the conventional dispersion only 5.2 %.

Parenteral Drug Delivery

The drug clofazimine is given as iv, the concentration in the liver, spleen and lungs reached a high level i.e.; greater than minimum inhibitory concentration, for most of the mycobacterium avium strains. Tarazepide is formulated as nanosuspension in order to overcome the use of surfactants and cyclodextrins to improve the bioavailability.

Pulmonary Drug Delivery

Here we are using nano-preperations for the drugs which have poor solubility in pulmonary secretions. For the lung delivery it is nebulized by mechanical or ultrasonic nebulizer. E.g: budesonide.

Occular Drug Delivery

These mainly applied for hydrophobic drugs. It increases the residence time include sac. The best example of nanosuspension is ibuprofen. The antiinflammatory activity of ibuprofen increased compared with the aqueous preparation.

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.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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REFERENCES

1. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol.

2. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv Drug Del Rev.

3. Lenaerts VM, Gurny R. Gastrointestinal Tract- Physiological variables affecting the performance of oral sustained release dosage forms. In: Lenaerts V, Gurny R, eds. Bioadhesive Drug Delivery System. Boca Raton, FL: CRC Press; 1990.

4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res.

5. Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. US patent 3 507 952. April 22, 1970.

6. Davis SS, Stockwell AF, Taylor MJ, et al. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res.

7. Urguhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28, 1994.

8. Mamajek RC, Moyer ES. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.

9. Fix JA, Cargill R, Engle K. Controlled gastric emptying. III. Gastric residence time of a non-disintegrating geometric shape in human volunteers. Pharm Res.

10. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J Control Release.

11. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm.

12. Shaikh S., Merekar AN, Godge GR.* and Gaikwad MR, Formulation And In-Vitro Evaluation Of Buccal Mucoadhesive Tablets Of Catopril By Using Natural And Synthetic Polymers, World Journal of Pharmaceutical Research, Vol 5, Issue 7, 2016 pp. 1296-1315

13. Kute VC* and Godge G., Preparation & In-Vitro Evaluation Of Inclusion Complexes Of Simvastatin Tablet With Cyclodextrins World Journal of Pharmaceutical Research, Vol 5, Issue 2, 2016 pp. 1022-1041

14. Godge GR. et al, Formulation development and in-vitro evaluation of sustained release tablets of telmisartan by solid dispersion technology. Asian Journal of Pharmaceutical Technology & Innovation, 04 (17); 2016; 131-139.

15. Chemate SZ., Godge GR., Pawa KK. and Rupnar KA. Preparation and evaluation of hollow calcium pectinate beads for floating-pulsatile drug delivery. Turk J Pharm Sci 13(1), 91-102, 2016

16. Raskar MA*, Godge GR, Chitale AB and Giri PD,. Validated simultaneous spectrophotometric estimation of telmisartan, hydrochlorthiazide and amlodipine besylate in combined tablet dosage form. Der Pharmacia Lettre, 2015, 7 (11):120-124

17. Godge GR, *, Misal AV. and Pawar PY. Formulation And Evaluation Of Mouth Dissolving Tablet With Taste Masking Resin. International Journal of Life Sciences and Review, 2015; Vol. 1(7): 253-263.

18. Godge G*, Labade S and Misal A. Oral Bioavailability Improvement Using Solid Dispersion Techniques: A Review. International Journal of Life Sciences and Review, (2015), Vol. 1 (7): 243-252.

19. Hiremath S, Godge G*, Sonawale B and Shirsath R, Pharmaceutical Advances In Cyclodextrin Inclusion Complexes For Improved Bioavailability Of Poorly-Soluble Drugs International Journal of Pharmaceutical Sciences and Nanotechnology, Volume 8, Issue 3 July – September 2015, pp 2894-2905.

20. Godge GR* and Labade SP., Preparation Of Solid Dispersion Of Poorly Water Soluble Drug Formulation And Consideration. International Journal of Pharma Sciences and Research, Vol. 6 No.5 May 2015, pp. 897-903.

21. Godge GR,* and Hiremath SN. An Investigation into the Characteristics of Natural Polysaccharide: Polymer Metoprolol Succinate Tablets for Colonic Drug Delivery. Mahidol University Journal of Pharmaceutical Sciences 2014; 41 (2), 7-21.

22. Godge GR.* and Hiremath SN, Colon Targeted Drug Delivery System: A Review. Int. J. Pharm.Drug Ana. Vol: 2 Issue: 1 Page:35- 48.

23. Godge GR.* and Hiremath SN, Development and Evaluation of Colon Targeted Drug Delivery System by Using Natural Polysaccharides/Polymers. Dhaka Univ. J. Pharm. Sci. 13(1): 105-113, 2014

24. Hiremath S, and Godge G,* Preparation and in vitro Evaluation of Inclusion Complexes of Nelfinavir with Chemically Modified β-cyclodextrins. Dhaka Univ. J. Pharm. Sci. 11(2): 107-116, 2012 (December):107-116.

25. Godge G,* Hiremath S. Colonic delivery of film coated meloxicam tablets using natural polysaccharide polymer mixture. International Current Pharmaceutical Journal 2012, 1(9): 264-271.

26. Hiremath SN, Kharia AA, Godge GR. For Low Absorption Window Antihypertensive Agents. Research Journal of Pharmacy and Technology, Volume 03, Issue 01, January-March 2010

27. Hiremath SN. and Godge GR.* Recent Advances In Pharmaceutical Approaches to Colon Specific Drug Delivery. Pharm Tech, Oct-Dec 2011, Volume 2011, Issue 4, pp 1-8.

28. Kharia AA.*, Hiremath SN., Omray LK., Yadav R. and Godge GR. Gastro-retentive Drug Delivery System. Indian Drugs, May 2011, Volume 48, Issue 5, pp. 7-15

29. Hiremath SN*., Godge GR., Kharia AA., Vaidya VR. Studies On The Preparation, Characterization And Solubility Of B-Cyclodextrin-Nelfinavir Inclusion Complexes. JPRHC, July 2010, Volume 2, Issue 3, pp.279-284.

30. Vaidya VR, Karodi RS, Mohite MT, Hiremath SN, Godge GR. Formulation Optimization Of Mucoadhesive Buccal Tablets Of Carvedilol Using 32 Full Factorial Design. Deccan J. Pharmaceutics and Cosmetology 1(2): April-June 2010, pp 7-20.

31. Hiremath SN, Kharia AA, Godge GR., Formulation Strategies for Low Absorption Window Antihypertensive Agents. Research Journal of Pharmacy and Technology, Volume 03, Issue 01, January-March 2010.

32. Sanap D, Garje M, Godge G, Probiotics, their Health Benefits and Applications for Development of Human Health: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):631-640 http://dx.doi.org/10.22270/jddt.v9i4- s.3231