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NANOSUSPENSIONS: A NOVEL DRUG DELIVERY APPROACH

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ABSTRACT
Nanosuspension is a sub-micron colloidal dispersion of pure particles of drug stabilized by surfactants. Nanosuspensions can be produced such that nanocrystalsappear in final products. Drug Nanosuspensions can be used as intermediateproduct. Formulations of Nanosuspensions are most suitable for drugs with high log P value. Of the various methods like bottom up, precipitation and top down technologies, top down is the most preferred one. Particle size, size distribution and crystalline state are some of the important parameters to be considered while formulation of Nanosuspensions.
KEYWORDS: Nanosuspension, Nanocrystals, Homogenizer

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INTRODUCTION

Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. It is sub-micron colloidal dispersion of pure particles of drug stabilized by surfactants[1,2]. By formulating nanosuspensions, problems associated with the delivery of poorly water-soluble drugs and poorly water-soluble and lipid-soluble drugs can be solved. Nanosuspensions differ from nanoparticles[3], which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules) and from solid-lipid nanoparticles (SLN)[4], which are lipidic carriers of drug[5,6].

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. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect[7]. The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Ostwald ripening effect[8,9].

Table 1 gives an overview of the benefits of nanosuspension over conventional formulations[10].

Need for nanosuspension

Preparing nanosuspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value. 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[11].

Methods of preparation of nanosuspension

Preparation of nanosuspensions were reported to be a more cost effective and technically more simple alternative, particularly for poorly soluble drugs and yield a physically more stable product than liposomes; conventional colloidal drug carriers . Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols[12]) are called 'Bottom Up technology'. In Bottom Up Technology the drug is dissolved in a solvent, which is then added to nonsolvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The limitation of this precipitation technique is that the drug needs to be soluble in atleast one solvent and this solvent needs to be miscible with nonsolvent. The other method is 'Top Down Technologies[13,14], which include the disintegration

methods and are preferred over the precipitation methods. The 'Top Down Technologies' include Media Milling (Nanocrystals™), High Pressure Homogenization (HPH) in water (Dissocubes®), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (NANOEDGE™)[15,16]. Few other techniques used for preparing nanosuspensions are emulsion as templates, microemulsion as templates[12].Table 2. gives the summary of various technologies used in the preparation of nanosuspension.

ADVANTAGES OF NANOSUSPENSION

Physical Long-term Stability

Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is defined as the tendency for a particle dispersion to grow in diameter over time; by a process in which the smaller particles dissolve because of their higher solubility, with subsequent crystallization onto larger particles to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles. Ostwald ripening is totally absent in nanosuspensions due to uniform particle size, which is also responsible for long-term physical stability of nanosuspensions[12,17].

Increase in Saturation Solubility and Dissolution Velocity of drug

Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation (equation no.1), dissolution velocity increases due to increase in the surface area from micron size to particles of nanometer size.

$dx/dt = [(D \times A) / h] [Cs - X/V]$ ----------(1)

Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

According to the Prandtl equation, for small particles the diffusional distance h decreases with decreasing particle size. The decrease in h increases C_s (saturation solubility) and leads to an increase in gradient $(C_s-C_x)/h$ and thus to an increase in the dissolution velocity. According to Ostwald-Freundlich equation decrease in particle size below 1μm increases the intrinsic solubility or saturation solubility[12,17].

Internal structure of Nanosuspensions

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenization, particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenization cycles, chemical nature of drug and power density applied by homogenizer[12,17].

CHARACTERIZATION OF NANOSUSPENSIONS

The essential characterization parameters for nanosuspensions are as follows[18]:

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 nanosuspensions. It has been indicated that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug[19]. Photon correlation spectroscopy (PCS)[20]can be used for rapid and accurate determination of the mean particle diameter of nanosuspensions. Moreover, PCS can even be used for determining the width of the particle size distribution (polydispersity index, PDI). The PDI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PDI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PDI value greater than 0.5 indicates a very broad distribution.

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 nanosizing. Additionally, when nanosuspensions are prepared, drug particles in an amorphous state are likely to be generated. 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 calorimetry[21]. 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 nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension.

Saturation solubility and dissolution velocity

The determination of the saturation solubility and dissolution velocity is very important as these two

parameters together help to anticipate any change in the *in vivo* performance (blood profiles, plasma peaks and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter.

***In vivo* biological performance**

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.

APPLICATIONS OF NANOSUSPENSIONS IN DRUG DELIVERY

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 gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and / or dissolution rate limited absorption is believed to possess slow and/or highly variable oral bioavailability.

Parenteral drug delivery

From the formulation perspective, nanosuspensions meet almost all the requirements of an ideal drug delivery system for the parenteral route. Since the drug particles are directly nanosized, it becomes easy to process almost all drugs for parenteral administration. Hence, nanosuspensions enable significant improvement in the parenterally tolerable dose of the drug, leading to a reduction in the cost of the therapy and also improved therapeutic performance.

Ocular drug delivery

Nanosuspension can also be used for the drugs that exhibit poor solubility in lachrymal secretions. To achieve sustained release of the drug for a stipulated time period, nanosuspension can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts.

Pulmonary drug delivery

Nanosuspension can be used for delivering drugs that exhibit poor solubility in pulmonary secretions. Currently such drugs are delivered as suspension aerosol or as dry powder inhalers.

Targeted drug delivery

Nanosuspension can be used for targeted delivery as their surface properties and changing of the stabilizer can easily alter in vivo behaviour. Their versatility and ease of scale up and commercial production enables the development of commercially viable nanosuspensions for targeted drug delivery.Table 3 enlists certain currently marketed pharmaceutical products based on nanocrystalline technology.

CONCLUSION

Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose. Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water-and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies.

REFERENCES

1. Muller RH, GohlaS, Dingler A, Schneppe T. Large-scale production of solid-lipid nanoparticles and nanosuspension. Handbook of pharmaceutical controlled release technology; 2000. p. 359-375
2. Barret ER. Nanosuspensions in drug delivery. Nat rev 2000;3:785-796
3. Shobha R, Hiremath R, Hota A. Nanoparticles as drug delivery systems. Ind J Pharm Sci 1999;61:69-75.
4. Mehnertw, Mader K. Solid lipid nanoparticles: Production, characterization and applications. Adv Drug Deliv Rev2000;47:165-96.
5. N Arunkumar, M Deecaraman, C Rani. Nanosuspension technology and its application in drug deliver., Asian J Pharm 2000;3:168-173.
6. Pandey S, Devmurari V,Goyani M and Ashapuri H. Nanosuspension: Formulation, charcterization and evaluation. Int J Pharma Bio Sci 2010; V1:1-10.
7. RH Muller, C Jacobs, O Kayer. Nanosuspensions for the formulation of poorlysoluble drugs. In: F Nielloud, G Marti-Mestres (ed). Pharmaceutical emulsion and suspension, Marcel Dekker, New York; 2000. p. 383-407.
8. RA Nash. Suspensions. In: J Swarbrick, JC Boylan (ed). Encyclopedia of pharmaceutical technology, 2nd ed. vol. 3, Marcel Dekker, New York;2002. p. 2045-3032.
9. RH Muller, K Peters. Nanosuspensions for the formulation of poorly soluble drug I: Preparation by size reduction technique. Int J Pharm 1998;160:229-37.
10. Patil VB. Nanosuspensions: A Novel Approach In Drug Delivery. 2008[Online].http://www.pharmainfo.net/reviews/nanosuspensions-novel-approach-drug-delivery, accessed on September 5, 2009.
11. Patravale VB, Abhijit AD, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. J Pharm Pharmcol 2004;56:827-840
12. Kirpukar BK. Nanosuspensions in drug delivery: Technology and applications, Express Pharma Pulse 2005; 34-35.
13. Chowdary KPR, Madhavi BLR. Novel drug delivery technologies for insoluble drugs. Ind. Drugs 2005; 42:557-563.
14. Cornelia MK, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high-pressure homogenisation. Eur J Pharm Biopharm 2006;62:3–16
15. Muller RH, Bohm BHL, Grau J. Nanosuspensions : a formulation approach for poorly soluble and poorly bioavailable drugs, In D.Wise (ed.) Handbook of pharmaceutical controlled release technology 2000; p. 345- 357.

16. Chowdary KPR, Madhavi BLR. Novel drug delivery technologies for insoluble drugs. Ind Drugs 2005;42:557-563.
17. Chaubal MV. Application of formulation technologies in lead candidate selection and optimization. Drug Dis.Today 2004; 9:603-609
18. Research and development of nanoparticle characterization methods. [online] New Energy and Industrial TechnologyDevelopmentOrganizationhttp://www.nedo.go.jp/kankobutsu/pamphlets/08_5kankyo/nanoryuushi_e.pdf, accessed on September 3, 2009
19. Liversidge GG, Cundy KC, Bishop, JF, Czekai DA. Surface modified drug nanoparticles. US Patent5 1992; 145,684.
20. Lee RW, McShaneJ, Shaw JM, Wood RW, Shenoy DB. Particle size reduction. Water Insoluble Drug Formulation, 2nd ed., CRC Press, London; 2008. p. 485-487.
21. Muller BW, Muller RH. Particle size analysis of latex suspensions and microemulsions by photon correlation spectroscopy. J Pharm Sci 1984;73: 915–918

Table 1: Potential benefits of nanosuspension technology over other conventional formulation technologies for poorly soluble drugs

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

Table 2: Summary of the nanosuspension formation technologies and compounds produced in nanosuspension

Technology	Advantages	Disadvantages
Precipitation	Simple process Low cost equipment Ease of scale up	Growing of drug crystals to be controlled Solubility of drug in solvent
High pressure homogenization	Low product contamination Simple technique for dilute/concentrate nanosuspension Aseptic production possible	Possible contamination of product with metal ions from walls of homogenizer Very high number of homogenization cycle
Media milling	High flexibility in production Large batch production possible with minimal batch to batch variation	Long milling process with generation of residue of milling media
Emulsion/Microemulsion template	Ease of manufacture Long product shelf-life	Use of high quantity of surfactant and hazardous chemicals
Dry Co-grinding	Short grinding time No organic solvent	Generation of residue of milling media

Table 3: Current marketed pharmaceutical products utilizing nanocrystalline formation[45]

Product	Drug	Indication	Company	Nanoparticle technology
EMEND®	Aprepitant	Antiemetic	Merck	Elan drug delivery nanocrystals®
TriCor®	Fenofibrate	Treatment of hypercholesterolemia	Abbott	Elan drug delivery nanocrystals®
MEGACE®ES	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	Elan drug delivery nanocrystals®
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Elan drug delivery nanocrystals®
Triglide™	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical	Skye Pharma IDD®-P technology

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