Review Article

Nanosuspension Based Drug Delivery: A Key Discussion on its Present and Future Perspectives

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ABSTRACT

Nanosuspension can resolve the problem of poor aqueous solubility and bioavailability of drugs. Stability of the nanosuspension is very important property. It can be prepared by simple and economical methods. Nanosuspensions can be administered by different routes. Their incorporation to other dosage forms like oral thin films, in situ gel etc. can achieve targeted drug delivery. Nanosuspension signifies sufficient safety and efficacy. Various nanosuspensions of drugs are successfully marketed today. The main intention of the review is to discuss basic requirements, common problems, polymers used in formulation, methods of preparation, evaluation tests and applications of nanosususpensions.

Keywords: Nanosuspension, hybrid formulation, common problems, evaluation tests.

INTRODUCTION

At present, more than 65 % of marketed drugs are oral products. Oral route of administration is the most expedient and commonly used for drug delivery due to its ease of administration, high patient compliance, non-sterile nature, cost-effectiveness and flexible dosage forms but less bioavailability of poor water soluble drug is a major problem. It is also not suitable because of undesirable physicochemical and pharmacokinetic properties.[1-2] Therefore, low oral bioavailability is found in case of such drugs, which leads to high variability and poor control of plasma concentration and therapeutic effects.[2] Low aqueous solubility is one of the major current challenges faced by the pharmaceutical industry.[1] Solubility, dissolution and permeability of drug are rate limiting parameters for its oral absorption.[1] The large number of active pharmaceutical ingredients emerging from drug discovery process exhibits the same problem.[2] Various physicochemical and physiological parameters of drug affect the oral bioavailability of drug.[3] Size reduction of drug improves oral bioavailability of drug by increasing its effective surface area and thus increasing solubility and dissolution rate of drug.[1, 3-5] Dissolution is a process by which a solid substance goes into solution.[2-3] Solubility, dissolution and permeability of drug are rate limiting parameters for its oral absorption.[6] According to the Noyes and Whitney equation and Ostwald- Freundlich equation, increase in the effective surface area of drug is more accessible for the dissolution medium that fosters its aqueous solubility accordingly, thus leading to excellent bioavailability.[7] There is a challenge with the design of oral dosage forms that lies with their poor aqueous solubility and dissolution.[7] Various process and formulation parameters play a vital role for successful formulation of drug like solubility, stability, temperature, humidity, compatibility, speed of mixing, time of mixing etc.[7-8] Development of strategies to improve the aqueous solubility and dissolution rate of such drugs has become prerequisite.[8] Manipulation of drug properties is a more capable approach in pharmaceutical research than the development of new drug molecules and facing of above problems.[9-10] Delivery of the medicament at a proper rate and quantity to its site of action elicits the therapeutic effectiveness.[10] This attribute of the dosage form is referred to as physiologic availability, biologic availability or simply bioavailability.[11] For most of the drugs, the pharmacologic response is directly proportional to the bioavailability of the drug.[11]

Bioavailability is the rate and extent of a drug that reaches the systemic circulation. It is divided in two types:

a) Absolute bioavailability: It is the comparison of bioavailability of drug by non-intravenous administration with the bioavailability of the same drug following intravenous administration.

b) Relative bioavailability: It is the comparison of bioavailability of test drug to the reference drug by same route of drug administration.[12-13] Various pharmaceutical, physiological and physiological factors affect the bioavailability of drugs. Nanotechnology plays an important role in development of drug. It is a multidisciplinary scientific field undergoing vast development. It is an important strategy to deliver conventional drugs, recombinant proteins, vaccines and nucleotides.[14] Polymer based nanoformulations are widely used today. The modified physical and chemical properties of these products have attracted the researchers.[15] Nanosuspension is the novel approach to overcome the problem of low dissolution rate and compromised oral bioavailability and reduce the delivery issues by maintaining the drug in preferred crystalline state.[15-16] As

indicated by the Nernst-Brunner diffusion layer model, the peripheral layer of the solid particle breaks up rapidly into an adjacent thin portion of solvent.[16] Through that saturated film; steady state mass transfer takes place into the bulk solution.[16] It is proved an effective drug delivery system is to attain and maintain therapeutic plasma concentration of the drug.[4-5, 17-20]

NANOSUSPENSION

Nanosuspension is a biphasic, submicron, colloidal and stable dispersion of drug particles in aqueous vehicle.[20-21] Marketed nanosuspensions are generally administered through oral, topical, parenteral, ocular and pulmonary routes.[21] If the drug is insoluble in both aqueous and organic medium; nanosuspension is a suitable formulation approach.[21] The formulation can be achieved by top-down or approaches. Nanoprecipitation is one of the promising techniques for development of nanosuspension of low water soluble drug molecules.[21]

Basic requirements for drug to formulate its nanosuspension are: a) High log P value, b) High melting point and c) high dose. Drugs having log P value in the range of 1 to 3 show good passive absorption across lipid membranes, and those having greater than 3 or less than 1 have frequently poor transport mechanisms.[3] In the last 30 years, different strategies of nanonization of hydrophobic drugs commonly used to control their solubility and bioavailability related issues.[2-3] Nanosuspensions explore a wide range of applications. Passive drug targeting and high drug loading are important applications; can be achieved by nanosuspension.[12-14] Commercially stable nanosuspensions have been marketed by the use of techniques like media milling and high pressure homogenization.[22] Nanosuspension based patents as compared to other nanotechnology dependent formulations have extensive prospective of getting faster in the market.[23] Presently, efforts are being made to outspread their applications in site-specific targeted drug delivery.[23]

Common problems for nanosuspension:[1, 3, 17-18]

a) One of the drawbacks after nanosization of drug is its conversion to amorphous state. High speed of the stirrer and also the heat generation in the process is responsible for that change. The mobility of the drug in amorphous phase is higher as compared to crystalline phase; thus nanocrystals are more stable in nanosuspension. XRD study of freeze dried nanosuspension is important to evaluate the change of crystalline nature of the drug molecules.

b) Ostwald ripening is thermodynamically driven spontaneous process which causes aggregation of particles. System always tries to lower its overall energy. Molecules on the surface of small particle are energetically unfavorable. According to Kelvin's equation; these molecules have tendency to detach from the surface of small particle and goes into solution. When all particles do this, it increases the concentration of free molecules in the solution (Supersaturation). The free molecules have tendency to condense on the surface of larger particles. Hence all smaller particles shrink and larger particles grow. Ultimately overall average size will increase and the phenomenon is called as Ostwald ripening. Increased bulk solubility of drug and increased interfacial tension are directly proportional to Ostwald ripening. Also, the change of Gibbs free energy results in agglomeration or crystal growth due to Ostwald ripening to produce thermodynamically unstable nanosuspension.

Polymers used in development of nanosuspensions:

Adsorption of polymers onto the drug particle surface produces steric stabilization; whereas adsorption of charged molecules or ionic molecules creates electrostatic stabilization.[24] Molecular weight of a polymer is the important thermodynamic driving force for such adsorption on the surface of the particle.[24] Higher is the molecular weight; slower the rate of adsorption.[24] A wide range of synthetic and natural polymers are used to formulate nano-systems. Biodegradable polymers are more advantageous over other materials for use in drug delivery systems because of their biocompatible elimination from the body. They can be shaped into various shapes and sizes to get variety of applications. Generally selection of polymer is based on the polymer type, molecular weight, copolymer ratio and, the desired degradation/ erosion effect of the nanoparticles.

1. Natural polymers

Natural polymers are generally safe, economical, aqueous soluble and biocompatible with the human body as well as formulation components.[25] Mostly they can be converted into nanoparticles through denaturation or cross-linking.[25-26] Electrostatic neutralization is one of the processes of formation of nanoparticles by oppositely charged counter-ions against charged groups present in the material.[25-27] Various such polymers are extensively used in industry like gelatin, albumin, lecithin, alginate, dextran, chitosan, agarose etc. Eudragit RL100 (copolymer of acrylates) is insoluble at physiological pH values and has capacity of swelling, thus representing suitable for the controlled release dispersions of drugs.[25-29] Eudragit based polymeric suspensions have been proved as a valid carrier system for the desired ophthalmic release of various drugs.[25-29]

2. Synthetic polymers

Synthetic polymers show superior retention of chemical properties by nanoparticles. Various such polymers like Polystyrene, Poly (lactic acid) etc. are employed in the modification of drug delivery.[25-29]

3. Mucoadhesive polymers

It is very crucial to extend the time period of adhesion of drug to surface of eye for its maximum effectiveness. Mucoadhesive polymers can prolong the pre-corneal residence time of drug. Mucoadhesion is established due to physicochemical interaction of polymer with mucus layer of cornea; mostly due to hydrogen bonding of

hydrophilic groups. Sufficient corneal hydration is important to foster mucoadhesive association, drug diffusion and penetration. Some polymers swell by retaining water and prolong the mucoadhesion of system.The examples of mucoadhesive polymers are sodium alginate, poly vinyl pyrrolidone, pectin, methyl cellulose, hydroxy propyl cellulose, tragacanth, gelatin, ethylene glycol, carrageenan, polyvinyl acetate, chitosan, carbomer etc.[25-29]

Surfactants used in development of nanosuspensions:

Surfactants (SLS, SDS, Tween 80, Poloxamer 188 etc.) are beneficial in nanosuspension: (1) to increase wettability and penetrability of drugs; (2) to prevent precipitation of drug from; and (3) to increase apparent solubility from micelle formation. Micelle formation takes place at the concentration above CMC. They comprise of an internal center of gathered hydrophobic sections and an external hydrophilic shell filling in as a balancing out interface. Micelles solubilize particles of non-polar nature inside the micelle center while polar atoms could be adsorbed on the micelle surface.[25-29]

Methods of preparation of nanosuspension:

For the most part there are two strategies for making of nanosuspensions. The conventional strategies are called as 'Bottom Up methods' (generation of smaller particles by precipitation at molecular level) which are not suitable for the drugs having inadequate solubility in both aqueous and nonaqueous media. e.g. Nanoprecipitation method. The 'Top Down methods' (fracturing larger particles to smaller particles) are favored for such drugs. e.g. Media Milling. Two widely used common methods of preparation of nanosuspension are explained below.

1. **Nanoprecipitation Method**

Precipitation has been applied for years to preparation of submicron particles of the poorly aqueous soluble drugs. Typically, the drug is firstly dissolved in a solvent which then mixed with miscible anti-solvent containing surfactants. Rapid addition of a drug solution leads to sudden supersaturation of drug followed by nuclei formation and crystal growth with generation of ultrafine drug solids. Minimum particle size with low growth rate is necessary for stable nanosuspension. Temperature also plays a key role in crystal growth.[30]

2. **Media Milling**

Nanosuspensions are set up by utilizing high-shear media. The processing chamber accused of processing media, solvent, drug and excipients is turned at an exceptionally high shear rate under controlled temperatures for a specified time. Generally used processing medium is made out of zirconium oxide stabilized by yttrium. The high vitality shear powers are created because of the impaction of the processing media that convert microparticulate system to nanoparticles.

Evaluation of nanosuspension:

Nanosuspensions are evaluated for (Figure 1):

a. Particle size and size distribution
b. Morphology of particles
c. Zeta Potential
d. Compatibility of ingredients
e. Crystallinity of particles
f. Saturation solubility
g. Dissolution rate& bioavailability
h. Stability

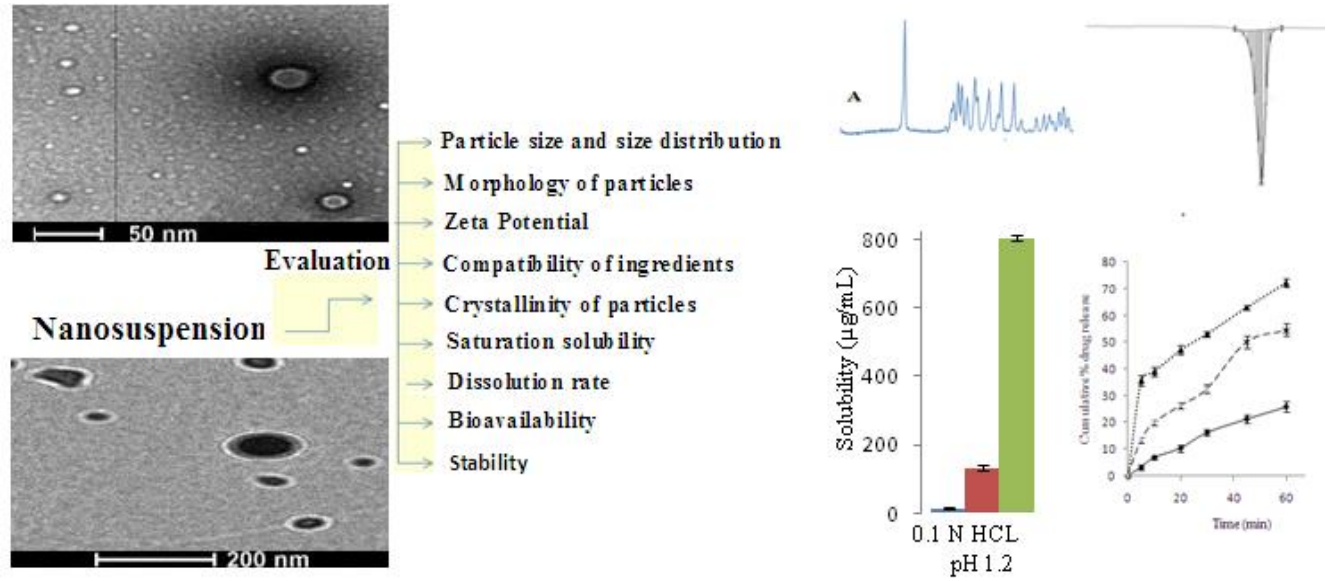

Figure 1: General evaluation tests for nanosuspension

a) Particle size and size distribution

The particle size and the polydispersity index (PDI) are important physicochemical parameters to control solubility and dissolution rate of drug. It can be evaluated by particle size analyzer.[31]

b) Morphology of particles

Polymorphic changes in the crystal of the drug can be detected by techniques like XRD, DSC, DTA, TEM etc. Surface morphology is very important to govern different properties.[3, 31-32]

c) Zeta potential

Zeta potential is the stability indicator of nanosuspension depending on the surface charge of particles.[32-34] Higher zeta potential values designate long term stability due to electrostatic repulsion between particles with same charges by preventing their aggregation. Required zeta potential for stable nanosuspension is ± 30 mV (electrostatic stabilization) and ± 20 mV (steric and electrostatic stabilization).[35] Flocculation takes place when the attractive forces exceed the repulsive forces. Zeta potential of formulation is measured by zeta meter.

d) Compatibility of ingredients

Analytical techniques like FTIR and DSC are employed to detect and ensure compatibility of ingredients in formulation.[3-5]

e) Crystallinity of particles

Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) are useful for determination of the crystallinity of particles. In nanosuspensions; there is the possibility of conversion of crystalline drug particle to amorphous form to certain extent.[3-5]

f) Saturation solubility

The nanosuspension increases the saturation solubility due to increased effective surface area of particles.[3-7] Saturation solubility is dependent on temperature and the composition of solvent.[3-7]

g) Dissolution rate & bioavailability

Improved dissolution velocity is one of the major benefits of nanoformulations. Dissolution study can be performed using different mediums and at different pH values. The parameters associated with dissolution profile of drug are proportional to in vivo activity of it. HPLC technique is widely used in assessment of bioavailability of drug after administration of prepared nanosystem of drug.[22-24]

h) Stability

Stability of nanosuspension is mainly dependent on particle size.[3] Smaller particles show high surface energy which may produce agglomeration.[3-5] Stabilizers like poloxamer, lecithin etc. are used to avoid such problems.[17-19]

1. Steric stabilization

Steric stabilization implicates the adsorption/attachment of non-ionic or amphiphilic polymers on the surface of drug particle by inhibiting aggregation.[3-4] The particles are kept at a distance from each other effectively because of mutual repulsion between stabilizing moieties.[3-4] Pluronic is a block co-polymer that liable for the hydrophobic interaction with the drug molecule. It is well known steric stabilizer. Crystal growth inhibition is mainly due to the hydrophobic polypropylene oxide group of that polymer.[36-37]

2. Electrostatic stabilization

The pH of the system is sensitive factor for its electrostatic stabilization.[36-37]

3. Electrosteric stabilization

Electrosteric stabilization is based on a combination of steric and electrostatic properties. e.g. Stabilization by surfactants with high molecular weight.[36-37]

Significance of nanosuspension:

Nanosuspension is extremely effective:[3-7]

- To improve stability of drug in the biological environment
- To mediate the bio-distribution of active molecules
- To improve drug loading
- For drug targeting
- For easy transport, release and exchanges with biological barriers
- To increase the saturation solubility and dissolution velocity of drug
- Can be lyophilized or spray dried to the nanoparticles for incorporation in a solid matrix

These advantages are summarized in Figure 2.

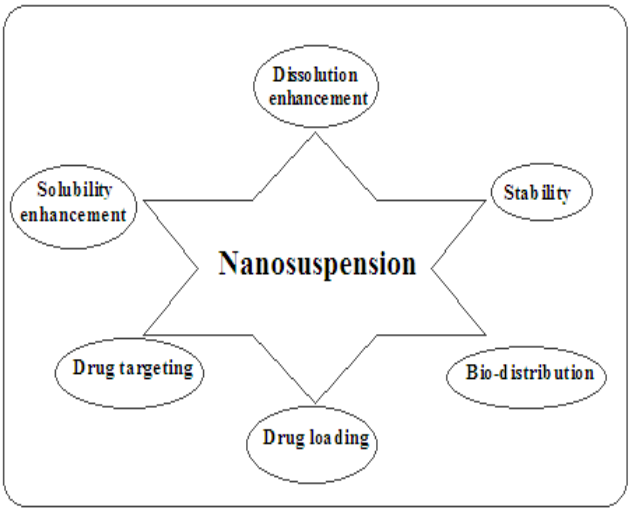

Figure 2: Advantages of nanosuspension of drug

Nanosuspensions can be more beneficial by following administrations:[22-26]

1. Oral drug delivery
2. Parenteral drug delivery
3. Targeted drug delivery
4. Ocular drug delivery
5. Pulmonary drug delivery

Alternative routes of administration are useful to improve the systemic availability of the drug by avoiding problems like first-pass metabolism, drug efflux by p-glycoprotein, interaction with food, enzymatic reaction and chemical reactions in GIT.[8-10]

Dual drug delivery by incorporation of nanosuspension:

There are different strategies can be applied regarding the incorporation of nanosuspension into other forms like:

1. Nanosuspension loaded oral thin film

Oral route is the most suitable, economical, and common route for drug delivery due high patient compliance and flexibility in the development of dosage form.[1-3] Many drugs exhibit poor aqueous solubility, and oral bioavailability.[38-39] Oral thin film (OTF) is a novel dosage form similar to postage stamp in size, shape, and thickness (Figure 3). These undergo quick disintegration when placed in the mouth without water ingestion or mastication; thus OTF are safe from instability due to pH variations, and enzymes in GI tract.[38-40] Oral thin films have potential for stabilization of nanosuspension with improved drug release.[41-43] High viscosity of the film prevents aggregation of nanoparticles and drying enhances stability.[40-43] Such modified formulation, without changing the chemical structure of drug; are significant to produce quick onset of action during emergency circumstances.

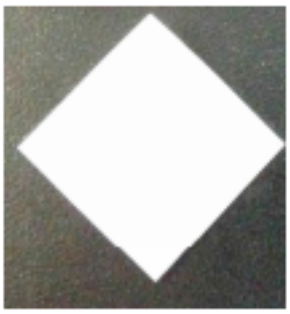

Figure 3: Oral thin film

2. Nanosuspension loaded *in situ* gel for ophthalmic administration

The eye is well known for its intricate structure and reluctant for entry of foreign substances comprising drugs.[4-5] Both segments (anterior and posterior) of the eye vary in anatomical and physiological aspects but work together against ocular application of product (Figure 4).

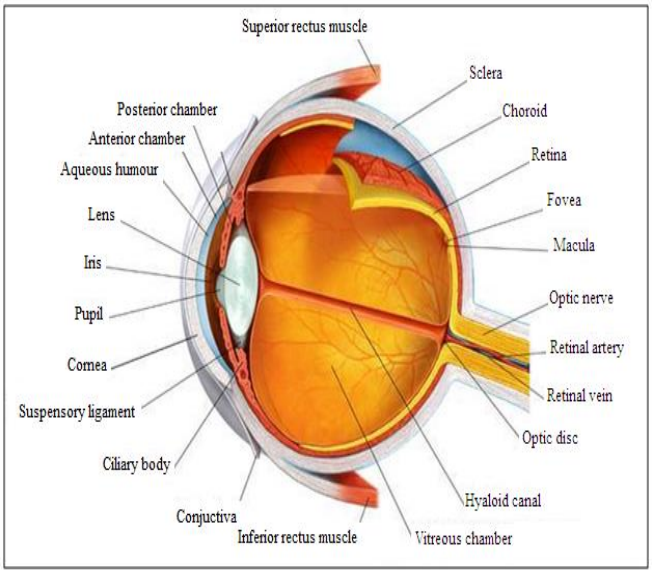

Figure 4: Anatomy of human eye

Generally the basic problems for topical application in the treatment of ocular infection is drug loss from pre-corneal surface, conjunctival uptake due to poor bioavailability and rapid drainage through naso-lacrimal areas.[4-5] However, short pre-corneal contact time combined with corneal impermeability result in low bioavailability, and frequent dosing is usually needed.[17] The defensive mechanism of the eye is one of the reasons of drug loss. Easy and rapid removal of drug from eye surface is possible due to eye blinking, lachrymation, tear turnover, naso-lachrymal drainage; that leads to sub-therapeutic drug levels at the target, predominantly at retina. Normally human eye can hold about 25–30 µl of an ocular solution.[42-44]

Delivery of drugs to the posterior eye is not easy; around 1% of total dose reaches to the aqueous humor. Five distinct layers of cornea contribute limited permeability and absorption of drug. Topical route signifies a safe administration comparative to other routes in treatment of ocular diseases, therefore the researchers trying to overcome the barriers and reach the goal.[44] Obviously there is a solid case for planning visual conveyance frameworks by concentrating on improved ocular bioavailability and expanded medication impact in focused tissues. The profoundly touchy corneal/conjuctival tissues towards infiltration enhancers to amplify medication transport require extraordinary alert in the determination of the enhancer. An elective methodology is to build up a medication conveyance framework that would evade the issues related with the traditional frameworks, and give the benefits of focused conveyance of medications for broadened timeframes and be quiet amicable.[44-45]

The last essential turns out to be increasingly urgent in situations where the patient needs to utilize the medication arrangement for an amazing duration, for example in glaucoma.[45] Nanosystems may sustain drug release and retain therapeutic levels for prolonged time period.[46-50] Such systems showed better stability and particle size distribution, and a positive surface charge making them

potential ophthalmic drug delivery systems. Particularly, positive surface charge (zeta potential) of these systems can prolong the residence time on the corneal surface, make sure slow drug release and higher drug concentration in aqueous humor.[51-54] In recent years; researchers have made significant effort in the development of novel ocular drug delivery systems like hydrogels, microparticles, nanoparticles, liposomes, solid inserts, shields, or polymeric implants.[55-57] Amongst them, nanotechnology is presently receiving a great attention in ocular drug delivery systems by the use of biodegradable and inert polymeric materials.[57-58]

Marketed Nanosuspensions:

Some marketed nanosuspensions (Table 1) are as follows:[47, 59-61]

Table 1: Marketed nanosuspensions

Drug	Brand Name	Company
Aprepitant	Emend	Merk
Fenofibrate	Tricor	Abbott
Fenofibrate	Triglide	First Horizon Pharma
Griseofulvin	Gris-PEG	Novartis
Megesterol acetate	Megace ES	Par Pharmaceutical
Nabilone	Cesamet	Lilly
Sirolimus	Rapamune	Wyeth
Paliperidone palmitate	InvegaSustenna	Johnson & Johnson
Paclitaxel	Abraxane	Abraxis Bioscience

CONCLUSION

Nanosuspension based drug delivery can be presented as dual/ hybrid formulation system (oral thin films, in situ gel etc.) to encounter various problems like stability and poor bioavailability of drugs and drugs. It can be prepared by simple and economical methods. Nanoprecipitation and media milling are commonly used methods for preparation of Nanosuspensions. It can be administered by different routes. Nanosuspension signifies sufficient safety and efficacy. Various nanosuspensions of drugs are successfully marketed today. Their basic requirements, common problems, polymers used in formulation, methods of preparation, evaluation tests and applications are discussed in this review.

REFERENCES

1. Verma S, Gokhale R, Burgess DJ, A comparative study of top-down and bottom-up approaches for the preparation of micro/nanosuspensions, Int. J. Pharm., 380, 2009, 216–222.
2. Doornbos CA, Haan PD, Encyclopedia of pharmaceutical technology, Swarbrick J, Boylan JC, Marcel Dekker, New York, 1995, 77.
3. Suresh S, Ahuja BK, Jena SK, Paidi SK, Bagri S, Formulation, optimization and in vitro–in vivo evaluation of febuxostat nanosuspension, Int. J. Pharm., 478, 2015, 540–552.
4. Shrivastava A, Sakthivel S, Pitchumani B, Rathore AS, A statistical approach for estimation of significant variables in wet attrition milling, Powder Technol., 211, 2011, 46–53.
5. Khalil RM, Kassem MA, Abdel Rahman AA, Ghorab MM, Ahmed MB, Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs, Int. J. Pharm., 340, 2007, 126–133.
6. Rowland M, Thomas N, Tozer, Clinical pharmacokinetic pharmacodynamics: concepts and applications, 4th edition, PA: Lippincott Williams & Wilkins, Philadelphia, 2010.
7. Sun J, Wang F, Sui Y, She Z, Zhai W, Wang C, Deng Y, Effect of particle size on solubility, dissolution rate, and oral bioavailability: evaluation using coenzyme Q_{10} as naked nanocrystals, Int. J. Nanomedicine, 7, 2012, 5733–5744.
8. Vyas SP, Khar RK, Targeted and controlled drug delivery: novel carrier systems, CBS Publishers, New Delhi, 2002, 331- 364.
9. Brahmankar DM, Jaiswal SB, Biopharmaceutics and pharmacokinetic a treatise, Vallabh Prakashan, New Delhi, 2015.
10. Witztum JL, Drugs used in the treatment of hyperlipoproteinemias, Goodman and Gillman's: The pharmacological basis of therapeutics, 9th edition, McGraw Hill, New York, 1996, 891-892.
11. Shargel L, Yu AB, Applied Biopharmaceutics & pharmacokinetics, 4th edition, New York: McGraw-Hill, 1999.
12. Govindarajan R, Nagarsenker MS, Formulation studies and in vivo evaluation of flurbiprofen-hydroxypropyl beta-cyclodextrin system, Pharm. Dev. Tech., 10, 2005, 105–114.
13. Heaney RP, Factors influencing the measurement of bioavailability, taking calcium as a model, J. Nutr., 131(4), 2001, 1344S-1348S.
14. Parveen S, Misra R, Sahoo SK, Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging, Nanomedicine, 8(2), 2012, 147-66.
15. Han J, Zhao D, Li D, Wang X, Jin Z, Zhao K, Polymer-based nanomaterials and applications for vaccines and drugs, Polymers, 31(10), 2018, 1-14.
16. http://www.in-adme.com/dissolution_theory.html
17. Ghosh I, Bose S, Vippagunta R, Harmon F, Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth, Int. J. Pharm., 409, 2011, 260-268.
18. Wang Y, Hu X, Chen X, Lin X, Zhang L, Tang X, Zhang Y, A combined bottom-up/top-down approach to prepare a sterile injectable nanosuspension, Int. J. Pharm., 472, 2014, 130–139.
19. Muller RH, Keck CM, Twenty years of drug nanocrystals: where are we, and where do we go?, Eur. J. Pharm. Biopharm., 80, 2012, 1-3.
20. Zhang X, Guan J, Ni R, Li LC, Mao S, Preparation and solidification of redispersible nanosuspensions, J. Pharm. Sci., 103, 2014, 2166–2176.
21. Cui F, Xia D, Quan P, Piao H, Sun S, Yin Y, Piao H, Preparation of stable nitrendipine nanosuspensions using the precipitation–ultrasonication method for enhancement of dissolution and oral bioavailability, Eur. J. Pharm. Sci., 40, 2010, 325–334.
22. Singh SK, Vaidya Y, Gulati M, Bhattacharya S, Garg V, Pandey NK, Nanosuspension: Principles, perspectives and practices, Cur. D. Deliv., 13(8), 2016, 1222-1246.
23. Modh N, Mehta D, Parejiya P, Popat A, Barot B, An overview of recent patents on nanosuspension, Recent Patents D. Deliv. Formulation, 8(2), 2014, 144-154.

24. Tuomela A, Hirvonen J, Peltonen L, Stabilizing agents for drug nanocrystals: Effect on bioavailability, Pharmaceutics, 8(2), 2016, 16.
25. Kocbek P, Baumgartner S, Krist J, Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drug, Int. J. Pharm., 312, 2006, 179-186.
26. Krause KP, Muller RH, Production and characterization of highly concentrated nanosuspensions by high pressure homogenization, Int. J.Pharm., 214, 2001, 21-24.
27. Muller RH, Hhilde GE, Increase of solubility of poorly soluble drug by transfer to dissocubes using high pressure homogenization, Proc. Int. Symp. Control. Rel. Bioact. Mater., 26,1999, 112-113.
28. Radtke M, Nanopure: Pure drug nanoparticles for the formulation for poorly soluble drugs, New Drugs, 2001, 62-68.
29. Dearans R, Atovaquone pharmaceutical composition, US Patent US 6018080, 2000.
30. Prabhakar C, Krishna KB, A review on nanosuspensions in drug delivery, Int. J. Pharma and Bio Sci., 2(1), 2011, 549–558.
31. Montasser H, Fessi AW, Atomic force microscopy imaging of novel type of polymeric colloidal nanostructures, Eur. J. Pharm. Biopharm., 54, 2002, 281–284.
32. Bujanakova Z, Dutkova E, Balaz M, Turianicova E, Balaz P, Stability studies of As_4S_4 nanosuspension prepared by wet milling in poloxamer 407, Int. J. Pharm., 478, 2015, 187-192.
33. Ravichandran R, Development of an oral curcumin nanocrystal formulation, J. Nanotechnol. Eng. Med., 3(4), 2013, 041007.
34. Khan MI, Madni A, Peltonen L, Development and in-vitro characterization of sorbitan monolaurate and poloxamer 184 based niosomes for oral delivery of diacerein, Eur. J. Pharm. Sci., 95, 2016, 88-95.
35. Scholer N, Krause K, Kayser O, Muller RH, Atovaquone nanosuspensions show excellent therapeutic effect in a new murine model of reactivated toxoplasmosis, Antimicrob. Agents Chemother., 45, 2001, 1771 –1779.
36. Herzberger J, Niederer K, Pohlit H, Seiwert J, Worm M, Wurm FR, Frey H, Polymerization of ethylene oxide, propylene oxide, and other alkylene oxides: Synthesis, novel polymer architectures, and bioconjugation, Chem. Rev., 116, 2016, 2170−2243.
37. Yousif E, Haddad R, Photodegradation and photostabilization of polymers, especially polystyrene: review, Springerplus, 2, 2013, 398.
38. Sievens-Figueroa L, Bhakay A, Jerez-Rozo JI, Pandya N, Romanach RJ, Michniak-Kohn B, Iqbal Z, Bilgili E, Dave RN, Preparation and characterization of hydroxypropyl methyl cellulose films containing stable BCS class II drug nanoparticles for pharmaceutical applications, Int. J. Pharm., 423, 2012, 496–508.
39. Kumar MP, Rao YM, Apte S, Formulation of nanosuspensions of albendazole for oral administration, Cur. Nanoscience, 4, 2008, 53-58.
40. Susarla R, Sievens-Figueroa L, Bhakay A, Shen Y, Jerez-Rozo JI, Engen W, Khusid B, Bilgili E, Romanach RJ, Morris KR, Michniak-Kohn B, Dave RN, Fast drying of biocompatible polymer films loaded with poorly water-soluble drug nano-particles via low temperature forced convection, Int. J. Pharm., 455, 2013, 93–103.
41. Lai F, Franceschini I, CorriasF, Sala MC, Cilurzo F, Sinico C, Pini E, Maltodextrin fast dissolving films for quercetin nanocrystal delivery: a feasibility study, Carbohydrate Polymer, 121, 2015, 217–223.
42. Fuhrmann K, Fuhrmann G, Recent advances in oral delivery of macromolecular drugs and benefits of polymer conjugation, Cur. Opinion Colloid Interface Sci., 31, 2017, 67–74.
43. Zhang X, Guan J, Ni R, Li LC, Mao S, Preparation and solidification of redispersible nanosuspensions, J. Pharm. Sci., 103, 2014, 2166–2176.
44. Bucolo C, Drago F, Salomone S, Ocular drug delivery: a clue from nanotechnology, Frontiers Pharmacol., 3, 2012, 1-3.
45. Patel A, Cholkar K, Agrahari V, Mitra AK, Ocular drug delivery systems: An overview, World J. Pharmacol., 2(2), 2013, 47–64.
46. Xu Y, Liu X, Lian R, Zheng S, Yin Z, Lu Y, Wu W, Enhanced dissolution and oral bioavailability of aripiprazole nanosuspensions prepared by nanoprecipitation/ homogenization based on acid–base neutralization, Int. J. Pharm., 438, 2012, 287-295.
47. Chen A, Shi Y, Yan Z, Hao H, Zhang Y, Zhong J, Hou H, Dosage form developments of nanosuspension drug delivery system for oral administration route, Cur. Pharm. Design, 21, 2015, 1-11.
48. Ige PP, Baria RK, Gattani SG, Fabrication of fenofibrate nanocrystals by probe sonication method for enhancement of dissolution rate and oral bioavailability, Colloids Surf. B. Biointerfaces, 108, 2013, 366–373.
49. Muller RH, Peters K, Becker R, Kruss B, Nanosuspensions for the I.V. administration of poorly soluble drugs: Stability during sterilization and long-term storage, Int. Symp. Control. Release Bioact. Mater., 22, 1995, 574-575.
50. Lipinski C, Poor aqueous solubility- An industry wide problem in drug discovery, Am. Pharm. Rev., 5, 2002, 82-85.
51. Rao GC, Satishkumar M, Mathivnan N, Rao EB, Advances in nanoparticulate drug delivery systems, Ind. Drugs, 41(7), 2004, 389-395.
52. Wong SM, Kellaway IW, Murdan S, Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles, Int. J. Pharm., 317, 2006, 61-68.
53. Gary GR, Nanosizing: A formulation approach for poorly water-soluble compounds. Eur. J. Pharm. Sci., 18, 2003, 113-120.
54. Parikh RK, Manusun SN, Gohel MC, Soniwala MM, Dissolution enhancement of nimesulide using complexation and salt formation techniques, Ind. Drugs, 2005, 149-154.
55. Jadhav KR, Shaikh IM, Ambade KW, Kadam VJ, Applications of microemulsion based drug delivery system, Cur. Dr. Del., 3(3), 2006, 267-273.
56. Patravale VB, Date AA, Kulkarni RM, Nanosuspensions: A promising drug delivery strategy, J. Pharm. Pharmacol., 56, 2004, 827-840.
57. Muller RH, Bohm BH, Grau J, Nanosuspensions: A formulation approach for poorly soluble and poorly bioavailable drugs, Handbook of Pharmaceutical Controlled Release Technology, 2000, 345-357.
58. Kocbek P, Baumgartner S, Krist J, Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drug, Int. J. Pharm., 312, 2006, 179-186.
59. Krause KP, Muller RH, Production and characterization of highly concentrated nanosuspensions by high pressure homogenization, Int. J. Pharm., 214, 2001, 21-24.
60. Muller RH, Jacobs C, Kayser O, Nanosuspensions as particulate drug formulations in therapy rationale for development and what we can expect for the future?, Ad. Drug Del. Rev., 2001, 47.
61. Yang H, Teng F, Wang P, Tian B, Lin X, Hu X, Zhang L, Zhang K, Zhang Y, Tang X, Investigation of nanosuspension stabilized by Soluplus to improve bioavailability, Int. J. Pharm., 477, 2014, 88-95.

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