Literature Review:

1. Adriana Pohlmannb ,Valeria Weiss et al,[2002] studied, a spray-drying technique was applied to dry nanocapsule and nanosphere suspensions prepared by nanoprecipitation of polyesters using SiO as adjuvant. Powders obtained from nanocapsules presented stable drug recoveries and morphological characteristics after 5 months.

2. Ana M.Cerdeira,MarcoMazzott, BrunoGander et.al,[2010] studied, the practically water-insoluble miconazole nanoparticle prepared by using surface active and polymeric excipients were tested for their stabilizing effects. For efficient milling, two Preformulation criteria had to be fulfilled: are relatively low contact angle(<70)and high dispersibility of the native drug particles in the milling medium Hydroxypropylcellulose(HPC-LF)in combination with sodiumdodecylsulfate(SDS) stabilized best the miconazole nanosuspensions. A design of experiments was used to achieve drug particle mean sizes of 140–170nm by varying the concentrations of miconazole (5 and 20%, w/w), SDS (0.05 and 0.2%, w/w), and HPC-LF (1.25 and 5%, w/w). experiments revealed that minimal 0.0125% SDS and 3.125% HPC-LF were required for miconazole nanogrinding and nanosuspension stabilisation.

3. Andrej Dolenc, Julijana Kristl ,et,al, [2009] prepared nanosuspensions of celecoxib, a selective COX-2 inhibitor with low water solubility, et.al produced by the emulsion-diffusion method using three different stabilizers (Tween® 80, PVP K-30 and SDS) and characterized by particle size analysis, dissolution testing, scanning electron microscopy imaging, differential scanning calorimetry and X-ray powder diffraction. Spray-dried nanosuspension was blended with microcrystalline cellulose, and compressed to tablets, and their tensile strength, porosity and elastic recovery of tablets were investigated. The crystalline nano-sized celecoxib alone or in tablets showed a dramatic increase of dissolution rate and extent compared to micronized. SEM images showed that the nanoparticle morphology was influenced by the choice of stabilizers.

4. Bernard V Eerdenbrugh, Ludo Froyen, et.al, [2008] studied, that the need for addition of matrix formers prior to drying is largely dictated by the hydrophobicity of the compound for which the nanosuspension is made,. It was found that compounds with a more hydrophobic surface resulted in agglomerates which were harder to disintegrate, for which dissolution was compromised upon drying. The same was found for compounds having higher log P values.

5. Bernard Van Eerdenbrugh, et.al,[2008] reviewed focuses on recent advances with respect to three topics considering drug nanocrystals. The first topic is nanosuspension stabilization. The
second part describes recent advances on miniaturization of nanosuspension production, to enable formulation screening during preclinical development. Finally, literature available on further nanosuspensions solidification is discussed, focussing on the maintenance of the preservation of the rapid dissolution properties of the nanocrystals after further downstream processing.

6. Colin W. Pouton[2006] reviewed that the fate of the formulated product can be predicted using a range of *in vitro* tests to investigate the effects of dispersion, digestion, and gastric emptying on the fate of the drug. It would be useful to establish standard test protocols, particularly in the case of the lipolytic digestion test for lipid formulations, so that bioavailability data can be better understood and compared from laboratory to laboratory.

7. Dhananjay S. Singare, Seshasai, et al.,[2010], studied, to identify and optimize formulation and process variables affecting characteristic and scale up of nanosuspension manufacturing process on bead mill considering industrial perspective. Box–Behnken design was used for this study. Formulation factors evaluated were ratio of polymer to drug and ratio of surfactant to drug.

8. Dongsheng Mou, Huabing Chen, et al.,[2010], studied, to enhance the oral bioavailability of itraconazole (ITZ) with dried drug nanosuspensions. The feasibility of using poloxamer 407 or HPMC (50cp) as stabilizers for preparing ITZ nanosuspensions by facile acid–base neutralization was investigated. Dried ITZ nanosuspensions were prepared by spray drying.

9. Gabrielle Pilcer, Francis Vanderbist, et al.,[2009], demonstrated the possibility of delivering formulations to the lungs that are made up of a mixture of nano and microparticles of the active drug. On the one hand, nanoparticles were used to coat micron-size particles and on the other hand, formulations composed of solely nanoparticles were produced in order to form easily dispersible and reproducible micron-size agglomerates of particles. These new carrier-free dry powders, with only a small amount of surfactant, present high lung deposition properties.

10. Hanafy A, Spahn-Langguth H, et al.,[2007], studied the bioavailability of the poorly soluble fenofibrate following oral administration was investigated in rats. Four formulations were tested: a nanosuspension type DissoCube®, one solid lipid nanoparticle (SLN) preparation and two suspensions of micronized fenofibrate as reference formulations, one suspension in sirupus simplex and a second in a solution of hydroxyethyl-cellulose in physiological saline.

11. Hany S. Ali M., Peter York[2010] studied, a hydrocortisone (HC) nanosuspension (NS) was developed using microfluidic nanoprecipitation as a recent, simple and cost effective bottom-up
technique of drug nanonization. For comparison, a second HC, NSwas prepared by top-down wet milling procedures. The produced nanosuspensions were characterized for particle size, shape and zeta potential. HC nanosuspensions of approximately 300 nm particle size were produced by adjusting experimental conditions of the two processing techniques.

12. **Harivardhan Reddy and R.S.R, Murthy.[2005]**, prepared etoposide-loaded nanoparticles with glyceride lipids and then characterize and evaluate the in vitro steric stability and drug release characteristics and stability. et al investigate the formation of lipid nanoparticles by melt emulsification and a high-pressure homogenization technique followed by spray drying of the nanodispersion. Factors influencing the nanoparticles formation and spray-drying process were determined and optimized. The nanoparticles were subjected to electrolyte induced flocculation test to determine their steric repulsion properties.

13. **Herbert Pompe and Rainer H. Muller[2004]**, studied, to show the feasibility of omeprazole stabilization using the DissoCubesw technology and to find optimal production parameters for a stable, highly concentrated omeprazole nanosuspension. The high performance liquid chromatography analysis has proved the predominance of the nanosuspensions produced by high pressure homogenization in comparison to an aqueous solution. et al stated that the production of nanosuspensions by high pressure homogenization is suitable for preventing degradation of labile drugs.

14. **Indrajit Ghosh, Sonali Bose, et.al,[2010]**, developed a nanosuspension of a poorly soluble drug by nanomilling process using wet media milling to achieve superior in vitro dissolution and high in vivo exposure in pharmacokinetic studies. A promising nanosuspension was developed with Vitamin E TPGS based formulation with particle size in the nano range.

15. **J.E. Kipp[2004]** reviewed, a brief introduction to the pharmaceutical technology of pure submicron drug particles in relationship to other dosage forms, and study examples are presented to underscore the potential benefits of this approach in parenteral delivery.

16. **Jacobs C., Kayser O. Muller R.H. [2000]** demonstrated that a long-term stable nanosuspension, when using a sufficient high concentration of surfactant, can be obtained. tried to improve the in vivo performance of poorly soluble drugs by reducing the particles size of the drug thus leading to an increased surface area and an increased dissolution velocity.

17. **Ji-Yeun Choi,, Chul Ho Park, Jonghwi [2008]** showed the effect of the molecular weight of a itraconazole and hydroxypropyl cellulose on particle size reduction. In principle, an increase in
molecular weight produces two counteracting effects: a decrease in the diffusion rate of chains and an increase in the physical adsorption of a polymer. Based on the results of our research, it appears that polymers of smaller molecular weight are more suitable than larger polymers for efficient nanocommination. This indicates that the kinetic aspects of molecular weight are important.

18. Joseph Wongand and rew Brugger [2008] reviewed various challenges associated with developing intravenous nanosuspension dosage forms. In addition, various formulation considerations specific to intravenous nanosuspensions as well as reported findings from various clinical studies have been discussed.

19. Kalle Sigfridsson and Sara Forssen[2007] studied, to find out if the three different formulations were comparable and safe to administer. The results indicate that AZ68 is absorbed at a lower rate for crystalline nanosuspensions compared to amorphous nanosuspensions and solution.

20. Kassema MA, and Abdel Rahmanb AA,[2007], confirmed that nanosuspensions differ from micro-crystalline suspensions and solution as ophthalmic drug delivery systems and that the differences are statistically, highly to very highly significant. The effect of particle size in the micron and nano-size ranges as well as the effect of viscosity of the nanosuspension on the ocular bioavailability was studied the results show that compared to solution and micro-crystalline suspensions it is a common feature of the three drugs that the nanosuspensions always enhance the rate and extent of ophthalmic drug absorption as well as the intensity of drug action.

21. Katy Margulis-Goshen, MSc, et.al,[2009], studied, a new method to prepare nanoparticles of a poorly water-soluble drug, simvastatin, by evaporation of all solvents from spontaneously formed oil-in-water microemulsions. Tablets containing the flakes of Simvastatin nanoparticles showed tremendous enhancement in dissolution profile compared with conventional tablets.

22. Lai F., Pini,E Angioni. G.et,al[2010], prepared orally disintegrating tablets (ODT) using nanocrystal formulations in order to optimise dissolution properties of lipophilic, poorly soluble drug piroxicam (PRX). Different nanocrystal formulations et al prepared using a high pressure homogenisation technique and poloxamer 188 as Stabilizer; et.al concluded that the improvement in PRX dissolution rate is mainly caused by the increased surface-to-volume ratio due to the submicron dimension of the drug particles.
23. Leena Peltonen, Johanna Aitta et al, [2004], improved the entrapment efficiency of a model hydrophilic drug substance, sodium cromoglycate, loaded inside polylactic acid nanoparticles by a modified nanoprecipitation method. The entrapment efficiency was modified by changes in the solvent selection, the amount of the model drug substance (sodium cromoglycate), solvent selection, the pH values of the outer and inner phases, and, finally, by the addition of salt to the aqueous phases. The stability of the drug substance after the most successful drug loadings was studied by x-ray diffraction methods.

24. Lei Gao and Dianrui Zhang [2007] studied, that formulation of ORI as a nanocrystal suspension has exhibited great success in dissolution rate and saturation solubility enhancement due to its size and enormous surface area. The HPH method was shown to be a simple and efficient technique for particle size reduction with the help of optimized stabilizers.

25. Libo Wu, Jian Zhang et al, [2010] reviewed that the physical and chemical stability of drug nanoparticles, including their mechanisms and corresponding characterization techniques. A few common strategies to overcome stability issues are also discussed. The significant challenges associated with stabilizer screening, adding a stabilizer or combination of stabilizers is still the most commonly used and preferred approach to enhance the stability of nanosuspensions. Development of self-stabilized nanosuspensions, although currently seen as very complicated and challenging, is expected to grow with the continuing advancement in the field of particle engineering.

26. Grau M.J., Kayser, O. et al, [2000] studied that the milling process by high pressure homogenisation for the production of drug nanoparticles is highly reproducible with regard to the mean size and width of the distribution of the bulk population, et al reported reproducibility of small scale production parameters (particle size, size distribution, content of microparticles) was exemplary studied for the drug RMKP22.

27. Langguth P. and Hanafy A. [2005] studied, that some nanosized drug delivery systems are suitable for improving the bioavailability of poorly water soluble drugs. In addition to particle size, the presence of surfactants in the formulations had a major impact on bioavailability parameters.

28. Patrice Tewa-Tagne, Stephanie Brianc on et al, [2007], studied, that the spray-drying technique interesting alternative to lyophilization in order to transform NC dispersions into a dry product. To date, little attention has been paid for the use of the spray-drying process to prepare
redispersible spray-dried NC. et al investigating the possibility to stabilise NC within soluble MP designed to further disintegration in aqueous medium and reconstitution of NC dispersions.

29. Prabhat R. Mishra, Cornelia et al. [2009], studied that Hesperetin nanosuspensions with a mean PCS diameter of 300 nm produced with the three stabilizers Poloxamer, Plantacare 2000 and Inutec. From the zeta potential measurements, Inutec and Plantacare stabilized nanosuspensions were stable with no change in PCS diameter and LD diameter 99%.

30. Puneet Sharma, Zoran D. Zujovic et al. [2010] showed that nanosuspensions of forms I and II were prepared using HPH. During the process, solid state transformations were observed in forms I and II as a function of pressure. The nanoparticles present in the final nanosuspensions were characterized as hydrate. Depending upon the stabilizer composition, the particle size distribution and the solubility of the milled sample varied.

31. Ambrus R., Szabó-Révész P. et al. [2009], studied, to improve the dissolution rate, the drug was formulated in a nanosuspensions by using an emulsion–diffusion method, high-pressure homogenization or sonication. Optimization of the technological parameters (organic solvents, stabilizers, homogenization procedure and recovery of particles) allowed the formation of nanosuspensions with a particle size of 200–900 nm.

32. Muller R.H. and Jacobs C. et al. [2001], reviewed the production of nanoparticles on a laboratory scale is presented and special applications are highlighted, for example, mucoadhesive nanosuspensions for oral delivery and surface-modified drug nanoparticles for site-specific delivery to the brain. The possibilities of large scale production, the prerequisite for the introduction of a delivery system to the market are also discussed.

33. Muller R.H. and Jacobs C. [2002] showed that it is possible to obtain a buparvaquone nanosuspension stabilised with different components suitable for oral administration. By incorporation of the nanosuspension into mucoadhesive hydrogels. The nanosuspensions/hydrogel systems were physically long-term stable over a period of 6 months as indicated by the unchanged particle sizes.

34. Dixit R.P. and Nagarsenker M.S. [2008], illustrated that the poorly water-soluble drugs with low and variable bioavailability formulated in the SNGs. Ezetimibe was conveniently formulated in emulsion and converted to SNG with colloidal silicon dioxide. The SNGs filled into hard gelatin capsules showed two to threefold increase in the dissolution rate as compared to plain drug filled capsules signifying its potential in improved delivery of lipophilic drugs.
35. **Rainer H. Muller and Katrin Peters [1998]** showed that high pressure homogenization used to formulate suspensions with particles in the nanometer range nanosuspensions. The degree of particle fineness in the nanosuspensions was found to increase with production pressure and number of cycles. Furthermore, the achievable degree of particle fineness is a function of the nature of the drug, as are the particle shapes of the investigated drugs.

36. **Sachin K.Singh, Srinivasan K.K., et.al. [2010]** studied that polymer concentration ratio of polymer to drug and milling speed play a significant role in controlling the zeta potential of nanosuspensions. The study also helped in identifying certain formulation and processing parameters, such as high polymer concentration and high milling speed, which may affect the manufacturing of nanosuspension at higher scale.

37. **Shradhanjali Basa, Thilekkumar Muniyappan, et.al. [2008]** studied that use of wet bead-milling technology coupled with fluidized spray-layering process is a viable approach capable of resolving many of the current issues associated with formulation development of poorly water soluble drugs. The approach of reducing particle size to nanometer range in the presence of stabilizers for enhancing oral bioavailability is an attractive approach for BCS II compounds drugs with dissolution rate limited absorption.

38. **Spomenka Simovic, He Hui, et.al. [2010]** demonstrated that the physico-chemical and biopharmaceutical properties of a new class of hybrid lipid–silica microcapsules that contain poorly soluble and weakly acidic drug (indomethacin) that electrostatically interacts with oleylamine (cationic lipid present as stabilizer). Microcapsules are based on Pickering emulsions as the initial templates and were fabricated by either spray drying or phase coacervation.

39. **Sudhir Verma, Diane J. Burgess, et.al. [2009]** studied on Quality by design (QbD) principles were explored to maximize the understanding of the unit operation of microfluidization, for the preparation of nanosuspensions using indomethacin as a model drug. In order of importance, milling time, microfluidization pressure, stabilizer type, temperature and stabilizer concentration were identified as critical parameters affecting the formation and stability of nanosuspensions. Interaction between homogenization pressure, temperature and milling time also significantly affected the nanosuspension particle size.

40. **Suzanne M. D'Addio, Robert, et.al. [2010]** reviewed the nucleation and growth of organic nanoparticles at high supersaturation. et.al present process considerations for controlling supersaturations as well as physical and chemical routes for modifying API solubility to optimize
supersaturation and control particle size, et al concluded with a discussion of post-precipitation factors which influence nanoparticle stability and efficacy in vivo and techniques for stabilization.

41. V. Jannin, J. Musakhanian, D. Marchaud et al [2008], reviewed in Lipid Based Drug Delivery (LBDD) has developed over the past decade fuelled by a better understanding of the multiple roles lipids may play in enhancing oral bioavailability, et al reviewed the recent approaches in selecting the most appropriate lipid system(s); methods for characterization of their behavior in vitro and in vivo; and the current formulation and processing techniques to obtain various solid dosage forms.

42. Vijaykumar Nekkanti, Raviraj Pillai, et al [2009] studied, wet bead milling process coupled with spray drying is a viable approach for developing a nanoparticle formulation of candesartan that provided enhanced drug solubility and dissolution. Enhancing dissolution rate correlates with faster absorption, improved bioavailability with reduced variability that could translate into improved therapeutic outcome.

43. Wei Li, Yonggang Yang RH, et al [2010] prepared nanosuspension and microsuspension by high pressure homogenization. Their crystalline state were evaluated by DSC and PXRD, and both evaluations indicated lattice energy of drug particles decreased with decrease of particle size, et al shown that particle size reduction could increase RH in vitro dissolution rate. The smaller the particle size, the higher the dissolution rate.

44. XueMing Li, Li Gu et al [2009], improved the dissolution rate and bioavailability of lipophilic of fenofibrate by nanosuspensions with melt emulsification method combined with high-pressure homogenization was adapted, and mixture of poloxamer188 and PVP K30 were selected as surfactants. The dissolution rate of fenofibrate nanosuspension was increased obviously, and the product was evaluated by pharmacokinetic characteristic in rats. The AUC0–36 h and Cmax of nanosuspensions were increased when compared with the reference formulations.

45. Yongmei Yin, Fude Cui et al [2010], prepared and characterized nitrendipine nanosuspensions to enhance the dissolution rate and oral bioavailability of this drug. Nanosuspensions prepared by the precipitation–ultrasonication method. The effects of five important process parameters, i.e. the concentration of PVA in the anti-solvent, the concentration of nitrendipine in the organic phase, the precipitation temperature, the power input and the time length of ultrasonication on the particle size of nanosuspensions were investigated systematically.