Literature review

1. Chong-Kook Kim et al, (2001) developed a solid dispersion system containing cyclosporin A (CsA) in order to improve the bioavailability of poorly water-soluble CsA. Solid dispersion systems that are spherical in shape (CsA–microspheres) were prepared with varying ratios of CsA/sodium lauryl sulfate/dextrin using a spray-drying technique. Their study demonstrates that the CsA–microspheres prepared with SLS and dextrin with improved bioavailability of CsA.

2. D.Q.M. Craig et al, (2003) investigated the structure and bioavailability of a-tocopherol dispersions in Gelucire 44/14. In this investigation they described the preparation, physical characterization and in vivo behavior of solid dispersions of a liquid nutraceutical, a-tocopherol, in Gelucire 44/14. In conclusion, the dispersion of the liquid drug in Gelucire 44/14 appeared to allow the dual advantages of the preparation of a solid formulation and improved bioavailability of this material.

3. E. Badens et al, (2009) Compared solid dispersions produced by supercritical antisolvent and spray-freezing technologies. The objective of this work was to improve its dissolution kinetics. Results revealed that SAS and SF processed formulations exhibited enhanced dissolution rates.

4. F. Fawaz et al, (1996) studied comparative bioavailability of pure powder of norfloxacin and its formulations in rabbits: aqueous solution, polyethylene glycol 6000 solid dispersions (PEG 6000 SD), beta-cyclodextrin (fl-CD) and hydroxypropyl- beta cyclodextrin (HP-fl-CD) complexes. Results showed that the extent of absorption was significantly smaller with powder of norfloxacin than with its formulations. Bioavailability was improved and significantly higher with CD and complexes SD than with powder, but the improvement was lower than expected.

5. F. Kedzierewicz et al, (1993) prepared Tolbutamide PEG 6000 solid dispersions as well as Tolbutamide P-cyclodextrin complexes with a view to increasing the bioavailability of this poorly soluble drug. Their results indicate that the absorption of Tolbutamide is not increased in comparison with either bulk powder or a solution of the drug. However, there are obvious differences in the kinetics of absorption.

bioavailability of nitrendipine microspheres, a sustained-release microspheres having solid dispersion structure were prepared in one step. They concluded that the sustained-release microspheres with solid dispersion structure improved the bioavailability of the water insoluble drug and prolonged the T value.

7. **G. V. D.Mooter et al, (2005)** investigated the performance of three new solid dispersion formulations of itraconazole in human volunteers in comparison with Sporanox®, the marketed form. Solid dispersions made up of itraconazole (40%, w/w) and HPMC 2910, Eudragit E100 or a mixture of Eudragit E100-PVPVA64 were manufactured by hot-stage extrusion and filled in gelatin capsules. The results indicated that hot-stage extrusion can be considered as a valuable alternative for manufacturing solid dispersions of itraconazole.

8. **H. G. Choi et al, (2010)** prepared Ibuprofen–Poloxamer 188 (P 188) binary solid dispersions (SD) with different drug loadings, characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), and evaluated for solubility, in vitro release, and oral bioavailability of ibuprofen in rats. Immediate and complete release of ibuprofen from SDs was found, it might be because of the reduction in the drug crystalline due to eutectic formation.

9. **H. G. Choi et al, (2007)** developed a novel sibutramine base-loaded solid dispersion with gelatin and HPMC and characterized for physicochemical properties and pharmacokinetics in beagle dogs. Various solid dispersions were prepared using a spray drying technique with hydrophilic polymers such as gelatin, HPMC and citric acid. Results revealed that the sibutramine base-loaded solid dispersion prepared with gelatin, HPMC and citric acid is a promising candidate for improving the solubility and bioavailability of the poorly water-soluble sibutramine base.

10. **N. Zerrouk et al, (2001)** investigated the effects of solid dispersion on the solubility, the dissolution rate and the pharmacokinetic profile of Carbamazepine. Solubility studies showed a linear increase in Carbamazepine solubility with the increase of PEG 6000 concentration. There is no marked difference between physical mixtures and solid dispersions for the enhancement of carbamazepine solubility by PEG 6000. Furthermore, their investigations have highlighted the interest of solid dispersions prepared at «near»-eutectic composition.

11. **N. Yuksel et al, (2003)** studied the in vitro and in vivo performance of the semi-solid dispersion prepared with Gelucire 44/14 and Labrasol into hard gelatin capsules (GL) for
enhancing the dissolution rate of the drug. The results of the in vivo study revealed that the GL dosage form would be advantageous with regards to rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired.

12. **P.C. Sheen et al, (1995)** formulated a poorly water-soluble drug in solid dispersions to improve bioavailability. The formulations were prepared by a melting method with water-soluble carriers in which is highly soluble. This result was attributed to the ability of the surfactant to increase the wettability and spreadability of the drug in a solubilized state once released in the gastrointestinal medium.

13. **P. Mansky et al, (2008)** developed an efficient method for screening solid dispersion formulations that are intended to enhance the dissolution of poorly soluble compounds. The method is based on miniaturization and automation of sample preparation by solvent casting, and dissolution testing, in a 96-well plate format, using less than 0.1 mg of compound per well.

14. **P. Costa et al, (2007)** confer that Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, for example, melting and solvent evaporation. They also discussed the recent advances related on the area of solid dispersions.

15. **R. O. Williams III et al, (2008)** prepared nebulized itraconazole nanoparticle dispersions with biocompatible stabilizers. A nebulized dispersion of amorphous, high surface area, nanostructured aggregates of itraconazole (ITZ):mannitol: lecithin (1:0.5:0.2, w/w) yielded improved bioavailability in mice. The ultra-rapid freezing (URF) technique used to produce the nanoparticles was found to molecularly disperse the ITZ with the excipients as a solid solution. The results revealed that bioavailability may be enhanced, by decreasing the particle size to accelerate dissolution and increasing permeation.

16. **S. Onoue et al, (2010)** developed a Novel crystalline solid dispersion of tranilast with high photo-stability and improved oral bioavailability. Crystalline solid dispersion of Tranilast (CSD/TL) was prepared by wet-milling technique with aim of improving physicochemical and pharmacokinetic properties. Results showed that the crystalline solid dispersion strategy would be efficacious to enhance bioavailability of TL with high photochemical stability.
17. **T.M. Serajuddin et al, (2004)** enhanced Bioavailability of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture. Two solid dispersion formulations of the drug, one in Gelucire 44/14® and another one in a mixture of polyethylene glycol 3350 (PEG 3350) with polysorbate 80, were prepared by dissolving the drug in the molten carrier. Results revealed that the bioavailability of this poorly water-soluble drug was greatly enhanced by formulation as a solid dispersion in a surface-active carrier.

18. **T. Xing et al, (2008)** prepared solid dispersion (SD) consisting of Nimodipine, Eudragit-E100 and Plasdone-S630 by hot-melt extrusion (HME). Compared with pure drug and physical mixture, the dissolution of NMD was enhanced dramatically (about 80% within 30 min). Adding the Nimodipine solid dispersion (NMD-SD) powder to a mixture of Plasdone-S630 and PEG400, and then transferring it to hard HPMC capsules, resulted in Nimodipine semi-solid capsules (NMD-SSC). The dissolution from NMD-SSC was increased further (about 95% in 20 min).

19. **W. N. Charman et al, (2000)** developed a non-solubilising solid dispersion formulation (polyethylene glycol 6000) and two solubilising solid dispersions (Vitamin E TPGS and a Gelucire 44:14:Vitamin E TPGS blend) containing the antimalarial, Halofantrine (Hf), for bioavailability assessment. Studies in fasted beagles showed that the solid dispersions afforded a five- to seven-fold improvement in absolute oral bioavailability when compared with the commercially available tablet formulation.

20. **Y. Chen et al, (2004)** designed solid dispersions using Pluronic F-68 as a carrier for improving the dissolution and bioavailability of ABT-963, a poorly water-soluble compound. The solid dispersion substantially increased the in vitro dissolution rate of ABT-963. Dosing of the dispersion to fasted dogs resulted in a significant increase of oral bioavailability compared with the conventional IR capsule formulation. These results show that solid dispersion is a promising approach for developing ABT-963 drug products.

21. **Z. P. Chen et al, (2010)** studied comparative pharmacokinetics and bioavailability of Quercetin, Kaempferol and Isorhamnetin after oral administration of Ginkgo biloba extracts, Ginkgo biloba extract phospholipid complexes and Ginkgo biloba extract solid dispersions in rats. The results showed that the bioavailability of Quercetin, Kaempferol and Isorhamnetin
in rats was increased remarkably after oral administration of GBP and GBS comparing with GBE. The bioavailabilities of GBP increased more than that of GBS.

22. **A.M. Rabasco et al, (1991)** studied Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions. The increase in dissolution rate can be considered to result from crystal size reduction and the solubilizing effect of polyethylene glycol 6000. An intrinsic effect of the carrier also increases the dissolution rate of diazepam, since a physical mixture of the same composition dissolves more slowly than the solid dispersions.

23. **C. S.Yong et al, (2010)** developed a novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes, various valsartan-loaded solid dispersions were prepared with water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS). Effects of the weight ratios of SLS/HPMC and carrier/drug on both the aqueous solubility of valsartan and the drug-release profiles of solid dispersions were investigated.

24. **F. Cilurzo et al, (2002)** prepared nine SD made of Nifedipine and a low viscosity hydroxypropyl methylcellulose (HPMC) in different ratio were prepared by means of spray-drying technique and their structure was studied. The prepared SD improved the NIF dissolution rate in comparison with that of commercial NIF or NIF/HPMC physical mixtures. Moreover, the concentration of NIF in the dissolution medium increased decreasing the NIF content.

25. **G. Trapani et al, (1999)** prepared Solid dispersions and physical mixtures of Zolpidem in polyethylene glycol 4000 (PEG 4000) and 6000 (PEG 6000) with the aim to increase its aqueous solubility. These formulations, indeed, showed almost two- to three-fold longer ataxic induction times suggesting that, in the presence of PEG, the intestinal membrane permeability is probably the rate-limiting factor of the absorption process.

26. **J. B. Mielck et al, (1997)** studied Interactions between Bendroflumethiazide and water soluble polymers. I. Solubility of Bendroflumethiazide in water from solid dispersions and formation of associates under climatic stress. The results revealed that Polyvinylpyrrolidone K 25 decreases the solubility of Bendroflumethiazide (BFMT) in water at 25°C at concentrations below 2% (w/v) at pH 7.1 and below 1% (w/v) at pH 1.95, and enhances it above these concentrations, while polyethylene glycol 6000 and Poloxamer 188 continuously enhance this solubility in concentrations up to 5% (w/v).
27. **J.C. DiNunzio et al, (2010)** formulated solid dispersion using hydrocortisone as a model temperature-sensitive active ingredient to study the effect of formulation and processing techniques. Low substituted hydroxypropyl cellulose, a high glass transition temperature control, showed that the material was unable to solubilize hydrocortisone. Manufacturing process control studies using hot melt extruded compositions of hydrocortisone and PVPVA showed that increased temperatures and residence times negatively impacted product potency due to decomposition.

28. **J.L. Dubois et al, (1996)** studied the effects of molecular weight of polyethylene glycols (PEGS) on the dissolution rates and crystallinity of its solid dispersions with indomethacin and phenylbutazone. The dissolution rates of both solid-dispersed drugs decreased as the molecular weight of PEG increased.

29. **K.V. R. Murthy et al, (2002)** studied Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine (NM). The advantages of MGK over the parent gum karaya (GK) were illustrated by differences in the in vitro dissolution profiles of respective solid mixtures prepared by co-grinding technique.

30. **M.T. Marín et al, (2002)** investigated the interactions of Flunarizine with polyvinyl pyrrolidone in solid dispersions, prepared according to the dissolution method using methanol as the solvent. Combinations of flunarizine/polyvinyl pyrrolidone of the following percentage proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40 and 80/20 (mean particle size of 0.175 mm). Results revealed that the solubility increase was greater in solid dispersions than in physical mixtures and the solubility in equilibrium for solid dispersions and physical mixtures at the same drug/polymer proportion showed significant differences (PB/0.05).

31. **M.J. Arias et al, (1996)** illustrated the usefulness of spray-drying as a resourceful procedure for preparing solid dispersions. The study in the solid state of the triamterene-D-mannitol system from 10 to 40% w/w drug included scanning electron microscopy (SEM), X-ray diffraction (DRX) and differential scanning calorimetry (DSC). Observation helps to explain the much better dissolution rates obtained for the spray-dried outputs.

32. **M.J. Arias et al, (1995)** studied dissolution properties and in vivo behavior of triamterene in solid dispersions with polyethylene glycols. The results have shown that there were no
significant differences between the three polyethylene glycols (PEGS) under test. The in vivo effectiveness of the different preparations was also investigated by means of the urinary volumetric excretion (UVE) - pharmacologic effect - and by the estimation of Kc, Tmax and MRT – pharmacokinetic parameters.

33. **K.V. Margarit et al, (1994)** prepared solid dispersions of Ketoprofen and polyethylene glycol 6000 (PEG 6000) and compared the dissolution kinetics of the dispersions with physical mixtures and pure drug. They concluded that the 10:90 solid dispersion displays the best dissolution kinetics of those tested.

34. **S. Torrado et al, (1996)** In this study, solid dispersion systems of the sparingly water soluble drug, albendazole (ABZ), were mixed with varying concentrations of polyvinyl pyrrolidone (PVP K12) in an attempt to improve the solubility and dissolution rate of ABZ. As expected, the albendazole dissolution rate, expressed as the dissolution efficiency, and also the solubility coefficient were increased when albendazole was mixed with PVP.

35. **T. Ozeki et al,(1999)**, prepared Solid dispersion composed of the poly(ethylene oxide) (PEO)-carboxyvinyl polymer (CP) interpolymer complex containing phenacetin (PHE) using nine grades of PEO having different molecular weights from 2000 to 4500000. Results indicated that it is feasible to control the medicine release from the PEO-CP solid dispersion by varying the molecular weight of PEO.

36. **T.M. Cham et al, (1996)**, prepared Solid dispersions containing 5%, 10%, 20%, 30% and 50% of nifedipine were prepared with polyethylene glycol (PEG) 6000 as carrier, respectively, by the fusion method. The initial values and faster rate of decrease of surface area during the dissolution process were markedly enhanced in the solid dispersions with lower contents of nifedipine (5% and 10%) due to the formation of high energy metastable (amorphous) states of the drug and differences in the particle sizes had little effect on the values of the available surface area and the dissolution of the drug.

37. **V. Tantishaiyakul et al,(1999)** prepared Solid dispersions of Piroxicam with PVP K-17 PF and PVP K-90 by solvent method. FTIR analysis demonstrated the presence of intermolecular hydrogen bonding between piroxicam and PVP in solid dispersions. These interactions reflected the changes in crystalline structures of piroxicam. The non-amorphous solid dispersions in PVP K-17 showed almost equally fast dissolution rates to amorphous dispersions in PVP K-90.
38. **V. D. Mooter et al, (2002)** studied Mechanism of increased dissolution of diazepam and Temazepam from polyethylene glycol 6000 solid dispersions. It was concluded that the reduction of the mean drug particle size by preparing solid dispersions with PEG6000 is limited and that the influence of the polymorphic behavior of PEG6000 (as observed by DSC) on the dissolution was negligible.

39. **W. Wu et al, (2008)** formulated solid dispersions of Silymarin (SM) with polyvinyl pyrrolidone (PVP) by a one-step fluid-bed coating technique. The results of the central composite design suggested that both PVP/SM ratio and coating weight gain affected the dissolution rate significantly. The results indicate that the fluid-bed coating technique has the potential use in the preparation of solid dispersions.

40. **Y. Huang et al, (2010)** developed a method which uses experimentally obtainable data to predict the complete phase diagram of drug–polymer solid dispersion systems, for the first time in literature. Felodipine–poly(acrylic acid) (PAA) solid dispersion was used as an example to illustrate the application of this method. In experiments, Felodipine was shown to be immiscible with PAA in almost the whole range of drug content at room temperature.

41. **Y. Kawashima et al, (2005)** prepared solid dispersion particles of indomethacin (IMC) with different types of silica, non-porous (Aerosil 200) or porous silica (Sylysia 350) by using spray-drying method. The results shown that Tte dissolution rate of IMC from the solid dispersion particles with Sylysia 350 was faster than that of Aerosil 200 irrespective of IMC content.