Literature Review

Jain Rajeev A. et al. 2000, prepared a novel in situ method for the preparation of injectable biodegradable poly (lactide-co-glycolide) (PLGA) microspheres for the controlled delivery of drugs. The effect of the different formulation variables on the characteristics of the novel drug delivery system (NDDS) was investigated such as the concentrations of polyethylene glycol 400 (PEG 400), the encapsulated drug, and the hydrophilic excipient (mannitol); the types of encapsulated drug (micromolecules and macromolecules such as protein) and vehicles (replacing triacetin and Miglyol 812 by triethyl citrate and soybean oil respectively). Also, the effect of formulation, process, and storage (15 days/48°C) conditions on the physical stability of the encapsulated protein was evaluated.

Sawant K.K. 2011, designed a nanoparticulate drug delivery system of OZ using PLGA for direct nose-to-brain delivery to provide brain targeting and sustained release. PLGA nanoparticles (NP) were prepared by the nanoprecipitation technique and characterized by entrapment efficiency, particle size, zeta potential, modulated temperature differential scanning calorimetry (MTDSC) and X-ray diffraction (XRD) studies. It is hypothesized that PLGA NP-based nasal delivery system of OZ would provide brain targeting and sustained release of OZ within the brain. This benefit would help to improve its clinical utility, decrease the dose and frequency of dosing, reduce side effects and improve therapeutic efficacy.

Agarwal Bharat B. et al. 2010, employed a polymer-based nanoparticle approach to improve bioavailability of Curcumin. It was encapsulated with 97.5% efficiency in biodegradable nanoparticulate formulation based on PLGA and a stabilizer polyethylene glycol (PEG)-5000. They demonstrated that curcumin-loaded PLGA nanoparticles formulation has enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo over curcumin.

Ravi Kumar M.N.V. et al. 2007, optimized Estradiol loaded PLGA nanoparticulate formulations resulting in improved oral bioavailability and sustained release of Estradiol by varying the molecular weight and copolymer composition of PLGA. Nanoparticles were prepared following emulsion–diffusion–evaporation method employing didodecyldimethyl ammonium bromide (DMAB) as stabilizer. The effect of polymer molecular weight and copolymer composition on particle properties and release behavior (in vitro and in vivo) has been reported.
Barbosa Carlos M. et al. 2005, developed and characterized two different nanosystems: nanospheres and nanocapsules, containing either xanthone (XAN) or 3-methoxyxanthone (3-MeOXAN), with the final goal of improving the delivery of these poorly water-soluble compounds. The xanthones-loaded nanospheres (nanomatrix systems) and nanocapsules (nanoreservoir systems), made of PLGA, were prepared by the solvent displacement technique. The nanoparticle formulations characteristics were determined such as particle size and morphology, zeta potential, incorporation efficiency, thermal behaviour, in vitro release profiles and physical stability at 4°C. Their nanospheres had a mean diameter < 170 nm, a narrow size distribution (polydispersity index <0.1), and a negative surface charge (zeta potential < K36 mV). Their incorporation efficiencies were 33% for XAN and 42% for 3-MeOXAN.

Venier-Julienne M.C. et al 2010, provided insight into the improvement of protein release from PLGA microspheres. As protein interactions with the polymer are one of the main causes of incomplete protein release, a two-dimensional model was developed to quantify protein adsorption onto the PLGA surface. In this model, the anti-adsorption effect of formulation components (additives in solution, additives blended with the polymer, or modified polymers) was studied.

Kissel Thomas et al. 2007, used fluorescein isothiocyanate labeled dextran (FITC-dextran 40, FD40) as a hydrophilic model compound to identify drug release from microspheres prepared by a WOW double emulsion technique. Influence of process parameters on microsphere morphology and burst release of FD40 from PLGA microspheres was studied. Internal morphology of microspheres was investigated by stereological method via cryo-cutting technique and scanning electron microscopy (SEM).

Burgess Diane J., Zolnik Banu S. 2008, developed two PLGA microsphere formulations, with different polymer molecular weights to determine whether an in vitro and in vivo relationship could be established for Dexamethasone release. A USP apparatus 4 was used for in vitro testing. The in vivo release kinetics and pharmacodynamic effects of Dexamethasone were evaluated using a Sprague Dawley rat model.

Venier-Julienne et al., 2008, focused on studies performed with microparticles of biodegradable polymers from lactic and glycolic acids. Usually, aspects concerning protein stability issues
during the encapsulation step are not addressed; nevertheless, they should be solved before studying the release as they might drastically influence the final protein release pattern.

Singh Sanjay et al., 2009, developed extended-release PLGA nanoparticles of Risperidone and thermal-responsive in situ gel containing Risperidone nanoparticles for parenteral (subcutaneous) delivery and to reduce the dose dependent extra pyramidal side effects of Risperidone. PLGA nanoparticles of Risperidone were designed by nanoprecipitation method using polymeric stabilizer (Poloxamer 407). The prepared nanoparticles were characterized for particle size by photon correlation spectroscopy and atomic force microscopy.

Chatterjee M. D. et al., 2010, presented study indicating the capability of PLGA nanoparticles in enhancing the tumor uptake of Letrozole. Letrozole (LTZ) incorporated PLGA nanoparticles were prepared by solvent displacement technique and characterized by transmission electron microscopy, poly-dispersity index and zeta potential measurement.

Veronique Preat et al., 2012, reviewed why PLGA has been chosen to design nanoparticles as drug delivery systems in various biomedical applications such as vaccination, cancer, inflammation and other diseases. Also focused on the understanding of specific characteristics exploited by PLGA-based nanoparticles to target a specific organ or tissue or specific cells.

Holgado M.A. et al. 2009, presented a novel synthesis technique based on the flow focusing (FF) technology is investigated for the preparation of green fluorescent protein (GFP)-loaded PLGA microparticles.

Sawant K. K. et al., 2010, prepared, optimized (using factorial design) and characterized sustained release nanoparticulate formulations of Rivastigmine tartrate (RT) using the biodegradable polymers, PLGA and PBCA as carriers. The pharmacodynamic performances of the nanoparticles (NPs) were evaluated for brain targeting and memory improvement in scopolamine-induced amnesic mice using Morris Water Maze Test. PLGA NPs were prepared by nanoprecipitation technique, while PBCA NPs were prepared by emulsion polymerization technique. Effect of key formulation variables on particle size (PS) and percentage drug entrapment (PDE) of NPs was studied by using factorial design.
Mohammed Aqil, et al., 2010, developed and evaluated a new colloidal system, that is, poly(dl-lactide-co-glycolide) (PLGA) nanoparticles for Sparfloxacin ophthalmic delivery, to improve precorneal residence time and ocular penetration. Nanoparticles were prepared by nanoprecipitation technique and characterized for various properties such as particle size, zeta potential, in vitro drug release, statistical model fitting, stability, and so forth. Microbiological assay was carried out against Pseudomonas aeruginosa using the cup-plate method. Precorneal residence time was studied in albino rabbits by gamma scintigraphy after radio labeling of Sparfloxacin by Tc-99m.

Jain Rajeev A. 2000, provided the various traditional and novel techniques (such as in situ microencapsulation) of preparing various drug loaded PLGA devices, with emphasis on preparing microparticles. Also, certain issues about other related biodegradable polyesters are discussed.

Li Hu-lun et al. 2008, carried out study is concerned with preparing PLGA nanoparticles loaded with voriconazole (PNLV), investigating the burst release and agglomeration of PNLV, and also evaluating antifungal efficacy of PNLV compared with voriconazole (VRC). The emulsion–solvent evaporation technique for nanoparticles and tests against fungi were carried out.

Schwendeman Steven. P., Wischke Christian, 2008, reviewed the basic principles and considerations to develop microparticles formulation of hydrophobic drugs. Challenges with the diversity of drug properties, microencapsulation methods, and organic solvents are evaluated in light of the precedence of commercialized formulations and with a focus on decreasing the time to lab-scale encapsulation of water-insoluble drug candidates in the early stage of drug development.

Veronique Preat et al., 2009, developed Cremophor® EL-free nanoparticles loaded with Paclitaxel (PTX), intended to be intravenously administered, able to improve the therapeutic index of the drug and devoid of the adverse effects of Cremophor® EL. PTX-loaded PEGylated PLGA-based were prepared by simple emulsion and nanoprecipitation.

Puleo D.A., Raiche A.T., 2006, developed a PLGA-based coating system for producing biologically-inspired delivery profiles. Protein-loaded microspheres were made from PLGA (50:50) terminated with carboxylic acid groups (PLGA-2A) blended either with more
Park Tae Gwan, Mok Hyejung, 2008, prepared PLGA microparticles encapsulating therapeutic proteins was prepared under a water-free formulation condition. Bovine serum albumin (BSA) and recombinant human growth hormone (rhGH) were homogeneously solubilized as nano-scale complexes in methylene chloride phase by using polyethylene glycol (PEG) as a complex-forming agent. The organic phase containing dissolved PLGA and PEG/protein complexes was directly spray dried to obtain PLGA microparticles encapsulating proteins.

Sinha V.R. et al. 2004, reviewed the various properties of chitosan to microencapsulate drugs. Various techniques used for preparing chitosan microspheres and evaluation of these microspheres has also been reviewed. Also includes the factors that affect the entrapment efficiency and release kinetics of drugs from chitosan microspheres.

Costa M.H. Bueno da et al. 2004, prepared Microspheres of polymers like PLGA and studied as a vehicle for controlled release vaccines. They require materials and processes that might change the protein antigenicity. Lactic acid is produced during microsphere degradation that occurs in tandem with protein liberation.

Watson Christopher J.E. et al. 2005, provided an overview of the different immunosuppressive agents currently used in solid organ transplantation. Also a historical perspective on the development of immunosuppression for organ transplantation is followed by a review of the individual agents, with a focus on their mechanism of action and efficacy. Steroids, anti-proliferative agents (azathioprine and mycophenolate), calcineurin inhibitors (cyclosporine and tacrolimus) and TOR inhibitors (sirolimus and everolimus) are discussed along with both polyclonal and monoclonal antibody preparations.

Josh Levitsky, Anjana A. Pillai 2009, focused on existing immunosuppressive agents for liver transplantation and considers newer medications on the horizon.

Mattos Angelo M. de et al. 1996, focused the pharmacology of agents used in the therapy of immunologic renal disease and in renal transplantation. It should be recognized that clinical
pharmacology and experience with newer agents is limited, and potential utility is based largely on experimental data.

**Vinks Alexander A. et al. 2011**, presented pharmacokinetic (PK) properties of Prednisolone, the metabolite of the prodrug prednisone, in cSLE patients and explore the relationship between PK properties and cSLE disease activity.

**Prausnitz Mark R., Choy Young Bin, 2011**, presented test whether the Rule of Five predicts drugs for delivery via non-oral routes, specifically ophthalmic, inhalation and transdermal. They assessed 111 drugs approved by FDA for those routes of administration and found that >98% of current non-oral drugs have physicochemical properties within the limits of the Rule of Five. Also concluded that although current non-oral drugs mostly have physicochemical properties within the Rule of Five thresholds, the Rule of Five should not be used to predict non-oral drug candidates, especially for inhalation and transdermal routes.

**Khan M. A. et al., 2002**, presented study to prepare and evaluate an optimized self-nanoemulsified tablet formulation and evaluated the effect of formulation ingredients on the release rate of Ubiquinone from its adsorbing solid compact. A three factor, three-level Box–Behnken design was used for the optimization procedure, with the amounts of copolyvidone (X1), maltodextrin (X2) and microcrystalline cellulose (X3) as the independent variables. The response variable was cumulative percent of Ubiquinone emulsified in 45 min with constraints on weight, flowability index, tensile strength, friability and disintegration time of the dry powdered emulsion and the resultant compact. Based on the experimental design, different Ubiquinone release rates and profiles were obtained.

**Ragonese R. et al. 2002**, described the use of the Box–Behnken experimental design to optimize the factors affecting the separation of ethambutol hydrochloride (EB), its impurity 2-amino-1-butanol and the internal standard (phenylephrine hydrochloride) in a CE method for a pharmaceutical tablet assay. The three factors studied simultaneously were: buffer pH, buffer concentration and applied electric field, each at three levels. The method was optimized with respect to three responses: resolution between peaks, theoretical plate count and the migration time of the EB peak.
USFDA Pharmaceutical Development Report Example on QbD for IR Generic Drugs, 2011, illustrated how ANDA applicants can move toward implementation of Quality by Design (QbD) in their generic product development.

Huang Jun et al. 2009, presented in-depth process understanding, and offer opportunities for developing control strategies to ensure product quality; a combination of experimental design, optimization and multivariate techniques was integrated into the process development of a drug product. A process DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs, and establish design space to ensure desired CQAs.

Yu Lawrence X. et al. 2008, discussed importance of Quality by design that it is an essential part of the modern approach to pharmaceutical quality. Also discussed quality by design for generic drugs and presents a summary of the key terminology. The elements of quality by design are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed. Agreement on these key concepts will allow discussion of the application of these concepts to abbreviated new drug applications to progress.