**Synopsis of the thesis titled**

# Design, Characterization and Evaluation of Polymeric and Solid Lipid Nanoparticulate Systems of Olanzapine for Enhanced Efficacy

Submitted in partial fulfilment
of the requirements for the degree of
**DOCTOR OF PHILOSOPHY**

by

**EMIL JOSEPH**

Under the Supervision of

**PROF. R. N. SAHA**


BITS Pilani
Pilani | Dubai | Goa | Hyderabad

**BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE, PILANI**
**2015**

The effectiveness of a drug delivery system is highly dependent on its ability to deliver the therapeutic agent selectively/preferentially to the target site. Delivering the therapeutic agents to brain is always a challenging task for the formulation scientists because of the presence of blood brain barrier, with tight junctions in the brain endothelial cells. The application of nanotechnology in drug delivery has opened the doors of new opportunities to formulation scientists for the better and effective delivery to brain. In the current research, studies were carried out to design and characterize polymeric/solid lipid nanoparticulate delivery systems to enhance the therapeutic efficacy of Olanzapine (OLN) with controlled release and preferential brain distribution. Also, selected formulations were evaluated for pharmacokinetic and biodistribution characters as well as efficacy and adverse effects in animal models.

To achieve this broad objective, research work was carried out in following stages:

- Suitable analytical methods were developed and validated for the estimation of OLN in bulk, formulations, in-vitro release, stability and bio-samples.
- Preformulation studies were carried out to assess the pH solubility profile, partition coefficient, stability of OLN in solution and solid state and selection of appropriate excipients for design of the delivery systems.
- Polymeric and solid lipid nanoparticles as delivery systems were designed and various formulation variables and physical characteristics of the formulations were optimized.
- In-vitro evaluation of designed formulations was carried out for determining particle size, morphology, drug entrapment and drug release properties.
- In-vivo pharmacokinetic and biodistribution studies of selected designed formulations were carried out in rats to assess pharmacokinetic and biodistribution profiles of OLN as pure drug and designed formulations.
- In-vivo efficacy and adverse effects studies were carried out for the same selected designed formulations in suitable animal models to assess the efficacy of designed formulations as compared to pure drug.

The total work has been presented in following chapters.

**Chapter 1: Introduction**

Extensive literature review on schizophrenia, antipsychotic medications, its limitations, novel drug delivery approaches for CNS active drugs, their advantages and importance of nanoparticulate systems in drug delivery have been presented in this chapter. A thorough review of polymeric and solid lipid nanoparticulate systems, their components and methods of preparation have also been presented. Various techniques reported for in-vitro characterization of these delivery systems are discussed extensively. Based on literature review, the objectives of the research work have been defined at the end of the chapter.

**Chapter 2: Drug Profile**

Profile of OLN and reported physicochemical properties, gathered from literature have been presented in this chapter. The pharmacological properties of drug with mechanism of action, therapeutic indications, tolerability and side effects were also discussed in detail. Various pharmacokinetic properties such as absorption, distribution, metabolism and elimination were presented. Moreover, various formulations of the drug currently available in market have been represented.

**Chapter 3: Analytical and Bioanalytical Methods**

As analytical methods are essential for the successful development of any kind of drug delivery systems, new UV-spectrophotometric and liquid chromatographic (analytical and bio analytical) methods, suitable for the current project, were developed in-house and successfully validated. The developed UV-spectrophotometric and liquid chromatographic methods were found to be highly selective, sensitive, accurate, precise and robust, for the estimation of OLN in bulk and formulations. These validated analytical methods were applied successfully for the analysis of drug during various preformulation, formulation and in-vitro evaluation studies. The bioanalytical methods developed were found to be highly sensitive and selective for the estimation of OLN in biological samples such as rat plasma and various organs. These bioanalytical methods were successfully applied for the estimation of OLN during in-vivo pharmacokinetic and biodistribution studies in rat for the pure drug and nanoparticulate formulations.

**Chapter 4: Preformulation Studies**

Preformulation studies help in several decisions making during formulation development of the drug product and provide a strong foundation for the development of a dosage form. Preformulation studies demonstrated that OLN exhibited a pH dependent solubility in different buffers with high solubility in acidic pH buffers and low solubility in basic pH buffers. Distribution coefficients in various buffers and dissociation constant were determined successfully. Solution state stability studies suggested that OLN was found to be more stable in acidic pH as compared to alkaline pH and degradation kinetics was found to be of first order. The solid admixtures of OLN with various excipients showed good stability during solid state stability studies. Results obtained for the drug-excipient compatibility studies by DSC, demonstrated no significant interaction with various excipients selected for the formulation development.

**Chapter 5: Formulation Design and Characterization**

In this chapter, studies on the formulation development of polymeric and solid lipid nanoparticulate systems of OLN have been presented. OLN-loaded nanoparticles were prepared successfully using nanoprecipitation and emulsification-ultrasonication techniques. These methods were easy, reproducible and they produced nanoparticles with narrow size distribution and good entrapment efficiency. The influence of different formulation variables such as polymer/solid lipid concentration, surfactant concentration and drug proportions on studied responses such as size, encapsulation efficiency and drug content were studied in detail. OLN-loaded nanoparticles prepared from selected biodegradable polymer/solid lipids sustained the release of drug for prolonged period of time (48-60 h) as found by the in-vitro release studies. Morphological studies by scanning electron microscopy have shown that both polymeric and solid lipid nanoparticles were spherical in shape with smooth surface. The formulations also exhibited high redispersibility after freeze drying and stability study results demonstrated good stability with no significant change in the drug content and average particle size and release characters for the formulations stored at frozen conditions for a period of 6 months.

**Chapter 6: Pharmacokinetic Studies**

Methods and results of in-vivo pharmacokinetic and biodistribution studies of selected batches of developed formulations of OLN are presented in this chapter. The study was performed on male Wistar rats with an Institutional Animal Ethics Committee approval (Protocol numbers: IAEC/RES/13/14/REV-2/17/16) as per guidelines prescribed by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and under the supervision of registered veterinarian. In the present study, pharmacokinetic and biodistribution characters of OLN from developed nanoparticulate formulations were compared with that obtained for pure OLN solution administered by intra-venous route. In-vivo pharmacokinetic and biodistribution studies in rat indicated that as compared to OLN solution, nanoparticulate formulations demonstrated higher AUC values along with prolonged residence time of OLN in the rat blood circulation. Increased plasma concentration levels of OLN for nanoparticulate systems indicated change in distribution profile of OLN. More importantly, the distribution of OLN to the brain was significantly enhanced with nanoparticulate systems with greater increased residence times for coated nanoparticulate formulations as compared with OLN solution. Biodistribution study showed low uptake of studied nanoparticulate systems by kidney and heart, thereby decreasing the possibility of nephrotoxicity and adverse cardiovascular effects. The results of pharmacokinetic and biodistribution study indicate that OLN-loaded nanoparticulate systems may be highly promising for preferential distribution of OLN with effective OLN concentrations in brain for prolonged period of time with better patient compliance. Moreover, good compatibility of developed nanoformulations in rats was observed without any undesirable effects, during the entire course of study. The delivery of OLN using developed polymeric/solid lipid nanoparticulate systems would be highly advantageous over the existing conventional formulations with preferential delivery to the site of action over extended period of time.

**Chapter 7: In-vivo Evaluation and Adverse Effects Studies**

In this chapter, evaluation of in-vivo efficacy and adverse effects of same selected batches of developed formulations of OLN were investigated in animal models. In-vivo evaluation and adverse effects studies of OLN-loaded nanoparticulate systems in animal model have demonstrated an improved therapeutic efficacy than pure OLN. The antipsychotic effect of OLN-loaded nanoparticulate systems was maintained for a

prolonged period of time. The adverse effects studies demonstrated a decreased extra pyramidal symptoms and inhibition in weight gain as compared to the pure OLN. From these preliminary data it can considered that the OLN-loaded nanoformulations could be effective in the treatment of psychotic disorders with minimum adverse effects. Further studies are necessary to investigate the exact mechanisms related to the findings of the study.

**Chapter 8: Summary and Conclusions**

In this chapter, consolidated conclusions of the entire work have been presented. The results obtained by the current research indicated the promising potential of OLN loaded nanoformulations for the highly effective treatment of psychotic disorders with minimum adverse effects. Current study also advocates significant future scope of work, where in, scale-up studies of the manufacturing process from lab scale to industrial scale have to be performed and optimized. More studies could be performed in order to find out the exact mechanism of preferential permeation of drug loaded nanoparticulate systems to brain. Further studies are necessary to investigate the exact mechanisms related to the findings of decreased adverse effects. In addition, studies need to be carried out for the optimized formulations in the diseased human subjects. This research work may be further extended by using several other CNS active drugs and polymers/solid lipids which are not yet investigated.