# Chapter 1

# Introduction

### 1.1 Background/Present knowledge

Schizophrenia is one of the most complex and challenging psychiatric disorders that cause disturbances in thinking, perception, and volition. Schizophrenia is a relatively common form of mental illness with a lifetime prevalence of 1% and an annual incidence of about 10-15 per 1,00,000 (Turner T., 1997). Generally the symptoms are divided into two classes: positive (reality distortion) and negative symptoms (psychomotor poverty syndrome). Each patient is different and would suffer from more or less of positive and negative symptoms. The positive symptoms e.g. delusions, hallucinations, excitement and disorganization are more easily identified, as compared to the negative symptoms. The negative symptoms include apathy, attentional impairment and poverty of speech that may be difficult to distinguish from either depression or the side effects caused by medication with typical antipsychotics.

Schizophrenia is a long time illness with most individuals requiring long-time medication. The health care costs of Schizophrenia are very high. The disease is chronic which affects people in their youth and often requires frequent hospitalization and hospital outpatient management. Approximately half of the Schizophrenic patients experience periods with severe depression during their course of illness. Consequently, the detection of depression syndrome is very important, as 7-10% of all Schizophrenic patients commit suicide.

### 1.2 Present therapy for Schizophrenia

The diagnosis of schizophrenia is just as complex as the medication to suppress the symptoms. There is no real cure against Schizophrenia and most patients are bound to medication for the rest of their lives. The drug of choice is more often a trade-off between clinical efficacy and Extra Pyramidal Syndromes (EPS) or other adverse effects. Antipsychotic agents are classified as typical antipsychotics and atypical antipsychotics. All typical antipsychotics are dopamine antagonists (Kane JM, 1996) and were the main stay of drug treatment for Schizophrenia and other psychotic disorders. Typical antipsychotics exhibit non-selective dopamine [$D_2$] receptor blockade and this is responsible for the commonly observed side effects. Atypical antipsychotics on the other hand, block both central serotonin [$5HT_2$] and dopamine [$D_2$] receptors. Concurrent blockade of both these receptors is thought to be effective in diminishing the severity of extra pyramidal side effects and in improving negative symptoms. Typical antipsychotics show only partial improvement in many patients and in general they produce less improvement in negative than positive symptoms. All typical antipsychotics produce EPS

to varying degrees. On the other hand, atypical antipsychotic drugs have an additional blocking action on serotonin receptors. They are more likely to relieve the negative symptoms of Schizophrenia, and are relatively free from the EPS seen with typical antipsychotics.

Results of clinical studies show a trend indicating superiority of atypical antipsychotics compared with the typical antipsychotics in medication adherence behavior and quality of life (Nicola O'Connell., 2000). One such clinical study shows 28% improvement in the medication adherence with patients on atypical antipsychotic therapy (Vorugini LNP et al., 2002). Another similar study with larger sample of out patients followed up 3 months after discharge reported a trend towards improved medication adherence behavior for patients with atypical antipsychotics compared with those on typical antipsychotics (Olfson M., 2000). Most physicians feel that high rate of relapse; hospitalization and suicidal behavior associated with untreated schizophrenia indicate that continuous antipsychotic treatment is the most likely solution to successful therapy. Generally schizophrenic patients have difficulty to comply with their medication regimen because of the nature of the illness. Therefore, a long acting injectable medication that does not require the patient to take the medication daily might increase compliance and substantially improve patient symptoms.

Medication non-compliance is a major barrier to better health outcomes for people with schizophrenia. Atleast 50% of out patients with schizophrenia stop their medication within a year of hospital discharge and this non-compliance is a major risk factor for relapse which may turn out to be more severe and dangerous (Babiker IE, 1986).The factors contributing to non-adherence behavior are lack of motivation, depressive states, lack of insight and unawareness of illness and need of its treatment, sociodemographic characteristics such as young age, being single and lack of family involvement, complex dosing regimens and lack of reasonable access to medication.

Wang and coworkers (Wang JS et al., 2004) in their findings reported that atypical antipsychotics (Olanzapine and Risperidone) are actively effluxed out of the brain by the transmembrane energy-dependent efflux transporter P-glycoprotein (P-gp) present on the luminal side (side facing the blood) of the blood brain barrier , thus failing to reach the brain in therapeutic concentrations. This finding that the brain penetration of Olanzapine is limited by P-gp may be a factor contributing to variability in dose requirements for this antipsychotic

drug. Thus the need for a drug delivery system that can bypass the P-gp efflux system is mandatory for the effective treatment of Schizophrenia using either Olanzapine or Risperidone. Research across the globe is focusing on the development of biodegradable drug delivery systems for controlling the drug release at the site of action. Targeting of these drug delivery systems to the site of action can be achieved by particle size and surface modification using suitable surfactants/polymers.

Nanosuspensions and solid lipid nanoparticles have caught the attention of various researchers in recent years for targeting applications. Nanosuspensions have the advantage over liposomes / nanoparticles as 100% drug loading is achieved with nanosuspensions. Solid lipid nanoparticles possess the advantage over liposomes that they being solid at room temperature provide more controlled release because of their inherent solid lipid matrix. Numerous reports are available on attempts to formulate stable aqueous nanosuspensions and solid lipid nanoparticle dispersions. These formulations are highly unstable in dispersion state and normally lyophilization/ spray drying process is required to recover the nanoparticle in the powder form. Inspite of their various advantages, nanosuspensions and solid lipid nanoparticles have not been explored much as a drug delivery system to the brain.

This thesis work was designed to explore the possibility of improving the therapeutic efficacy of antipsychotic agents using PLGA microsphere based depot/ nanosuspension/ lipid nanoparticle systems. We also intended to investigate the effect of the route of administration of the formulated nanoparticles on the brain concentrations and biodistribution of the antipsychotic drug and identify the superior route of administration for the delivery of drug to the brain. Radiolabeling studies were performed (after establishing the invitro stability of the radiolabelled complexes) to study the blood clearance times and biodistribution of the plain drug and the nanoparticle formulations.

### 1.3 Objectives of the present work:

The prime objectives of this research work are as follows:

- Formulation of biodegradable polymeric (poly lactide co-glycolide) microparticles for intramuscular depot administration and study the basic parameters which affect drug incorporation, physical characterization and in vivo evaluation.
- Formulation of drug nanosuspensions for parenteral (both intravenous and intramuscular) administration by pearl milling technique, physical characterization and in vivo evaluation.
- Formulation of lipid based drug delivery systems (nanoparticles) containing antipsychotic agents with biocompatible lipids, optimization, characterization and in vitro evaluation.
- Radiolabeling and optimization of antipsychotic agents, drug loaded lipid nanoparticles.
- Pharmacokinetics and Biodistribution studies of drug loaded solid lipid nanoparticles after different routes of administration in rats.

### 1.4 REFERENCES

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