INTRODUCTION

1.1. NEED FOR NOVEL DRUG DELIVERY

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. Novel drug delivery methods offer substantial clinical advantages, including reduced dosing frequency therefore, improved patient compliance, minimized fluctuation of the concentrations and maintenance of blood levels within a desired range, localized drug delivery and potential for reduced adverse effects. The past twenty five years have seen an explosion in the creation and discovery of new novel drug delivery methods. Related innovations in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but have also permitted the development of new medical treatments with existing drugs. The creation of transdermal drug delivery systems (TDDS) has been one of the most important of these innovations, which is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. Delivering medicine to general circulation through the skin has been seen as desirable alternative to taking it by mouth (Scheindlin, 2004). It has been observed that many psychotropic drugs are non compliant because of large and diverse array of adverse effects and drug adherence problems and transdermal drug delivery may be useful in achieving patient compliance (David et al., 2003; Parikh et al., 2005). So transdermal delivery offers convenience and such a simple dosing regimen can aid in patient adherence to drug therapy. TDDS offers many advantages over conventional injection and oral methods (Prausnitz et al., 2004; Chein, 1992; Gordon and Peterson, 2003):

- Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery as it avoids direct effects on stomach and intestine.
- Drugs that are degraded by enzymes and acids in gastrointestinal tract (GIT) may also be good targets.
First pass metabolism, an additional limitation to oral drug delivery can be avoided with transdermal administration.

Steady permeation of the drug across the skin to obtain consistent serum drug levels can be achieved using transdermal drug delivery.

Drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery with reduced plasma peaks.

The active ingredients currently available on the market in the form of transdermal devices are fentanyl for moderate or severe pain, nitroglycerine for angina pectoris, nicotine for smoking cessation, testosterone for hypogonadism in males, clonidine for hypertension, lidocaine as anaesthetic, scopolamine for motion sickness, estrogen/progesterone for hormone replacement therapy, norelgestromin / estradiol for birth control and estradiol for postmenstrual syndrome (Berliner et al., 2007; Henzl and Loomba, 2003; Poltaski and Petros, 2005; Scheindlin, 2004; Kandavilli et al., 2002). In addition, drugs like rivastigmine for alzheimer’s and parkinson dementia, rotigotine for parkinsonism, fentanyl iontophoretic for patient controlled pain management, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are approved as TDDS (Rios et al., 2007). US FDA approved the first transdermal patch in 1981. This patch delivered scopolamine, a drug which suppresses nausea and vomiting in motion sickness (Gordon and Peterson, 2003). Over the last two decades, more than 35 transdermal products have been approved generating increase in sale day by day sale. This rapid increase in market value has led to transdermal drug delivery becoming one of the fastest growing sectors within pharmaceutical industry (Henzl, 2002; Frost and Sullivan, 2003; Brown et al., 2006). Currently, market growth is fuelled by the launch of new products within existing applications such as hormone replacement and pain management therapies. The introduction of Androgel, the first transdermal testosterone gel, resulted in unprecedented growth of this segment in a short span of time, clearly demonstrating the available market potential (Villaneueva et al., 2007). A rich area of research in India as well as abroad has been focused on developing transdermal technologies. There are a very few studies wherein the transdermal drug delivery systems has been exploited for psychotropic drugs.
1.2. SCHIZOPHRENIA

Mental illness has always been a part of the human experience and so has the quest to understand and treat it. As in other medical fields, the preferred treatments for mental illness have gone hand in hand with changing theories about its causes (Engstrom and Honey, 1997; Gurvich and Cunningham, 2000). However pathophysiology of mental illness is not clear, though some ideas have been formed, e.g. dopaminergic overactivity in the limbic system may be involved in schizophrenia and deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain may underlie depression. Conversely mania is caused by an overproduction of these neurotransmitters and anxiety occurs due to abnormal functions in several neurotransmitter systems, including norepinephrine, γ-aminobutyric acid (GABA) and serotonin. Treatment is empirical, symptom oriented, and not disease specific, however can be highly effective in many situations.

Psychosis, in particular schizophrenia, has been called the worst mental disease affecting mankind (Samanta et al., 2003). Schizophrenia is a chronic, severe, and disabling brain disease. Approximately 1% of the population develops schizophrenia during their lifetime. Although schizophrenia affects men and women with equal frequency, the disorder often appears earlier in men, usually in the late teens or early twenties, than in women, who are generally affected in the twenties to early thirties.

People with schizophrenia often suffer terrifying symptoms such as hearing internal voices not heard by others, or believing that other people are reading their minds, controlling their thoughts, or plotting to harm them. These symptoms may leave them fearful and withdrawn. Their speech and behaviour can be so disorganized that they may be incomprehensible or frightening to others. World of people with schizophrenia includes distorted perceptions of reality, hallucinations and illusions, delusions, disordered thinking and emotional expression.

1.2.1 Symptoms of schizophrenia

The symptoms of schizophrenia fall into three categories: positive symptoms, negative symptoms and cognitive symptoms

Positive symptoms

Positive symptoms are psychotic behaviors not seen in healthy people. People with positive symptoms often "lose touch" with reality. These symptoms can come
and go. Sometimes they are severe and at other times hardly noticeable, depending on whether the individual is receiving treatment. They include the following:

**Hallucinations** are things a person sees, hears, smells, or feels that no one else can see, hear, smell, or feel. "Voices" are the most common type of hallucination in schizophrenia. Many people with the disorder hear voices. The voices may talk to the person about his or her behavior, order the people to do things, or warn the person of danger. Sometimes the voices talk to each other. People with schizophrenia may hear voices for a long time before family and friends notice the problem.

**Delusions** are false beliefs that are not part of the person's culture and do not change. The person believes delusions even after other people prove that the beliefs are not true or logical. People with schizophrenia may believe that people on television are directing special messages to them, or that radio stations are broadcasting their thoughts aloud to others. Sometimes they believe they are someone else, such as a famous historical figure. They may have paranoid delusions and believe that others are trying to harm them, such as by cheating, harassing, poisoning, spying on, or plotting against them or the people they care about. These beliefs are called "delusions of persecution."

**Thought disorders** are unusual or dysfunctional ways of thinking. One form of thought disorder is called "disorganized thinking." This is when a person has trouble organizing his or her thoughts or connecting them logically. Finally, a person with a thought disorder might make up meaningless words, or "neologisms."

**Movement disorders** may appear as agitated body movements. A person with a movement disorder may repeat certain motions over and over. In the other extreme, a person may become catatonic. Catatonia is a state in which a person does not move and does not respond to others.

**Negative symptoms**

Negative symptoms are associated with disruptions to normal emotions and behaviour. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions. These symptoms include the following:

- "Flat affect" (a person's face does not move or he or she talks in a dull or monotonous voice)
- Social isolation
• Lack of pleasure in everyday life
• Attention deficit
• Speaking little, even when forced to interact.
• People with negative symptoms need help with everyday tasks. They often neglect basic personal hygiene. This may make them seem lazy or unwilling to help themselves, but the problems are symptoms caused by the schizophrenia.

Cognitive symptoms

Cognitive symptoms are subtle. Like negative symptoms, cognitive symptoms may be difficult to recognize as part of the disorder. Often, they are detected only when other tests are performed. Cognitive symptoms include the following:

• Poor "executive functioning" (the ability to understand information and use it to make decisions)
• Trouble focusing or paying attention
• Problems with "working memory" (the ability to use information immediately after learning it).

Cognitive symptoms often make it hard to lead a normal life and earn a living. They can cause great emotional distress.

1.2.2 Types of schizophrenia

There are five types of schizophrenia, each based on the kind of symptoms the person has at the time of assessment:

1) **Paranoid schizophrenia**: The individual is preoccupied with one or more delusions or many auditory hallucinations.

2) **Disorganized schizophrenia**: Prominent symptoms are disorganized speech and behavior, as well as flat or inappropriate affect.

3) **Catatonic schizophrenia**: The person with this type of schizophrenia primarily has at least two of the following symptoms: difficulty moving, resistance to moving, excessive movement, abnormal movements, and/or repeating what others say or do.

4) **Undifferentiated schizophrenia**: This is characterized by episodes of two or more of the following symptoms: delusions, hallucinations, disorganized speech or behavior, catatonic behavior or negative symptoms, but the
individual does not qualify for a diagnosis of paranoid, disorganized, or catatonic type of schizophrenia.

5) **Residual schizophrenia:** While the full-blown characteristic positive symptoms of schizophrenia (those that involve an excess of normal behaviour, such as delusions, paranoia, or heightened sensitivity) are absent, the sufferer has less severe forms of the disorder or has only negative symptoms (symptoms characterized by a decrease in function, such as withdrawal, disinterest, and not speaking).

### 1.2.3 Diagnosis of Schizophrenia

As is true with virtually any mental-health diagnosis, there is no one test that definitively indicates that someone has schizophrenia. Therefore, health-care practitioners diagnose this disorder by gathering comprehensive medical, family, and mental-health information. Patients tend to benefit when the professional takes into account their client's entire life and background. This includes but is not limited to the person's gender, sexual orientation, cultural, religious and ethnic background, and socioeconomic status. The practitioner will also either perform a physical examination or request that the individual's primary-care doctor perform one. The medical examination will usually include lab tests to evaluate the person's general health and to explore whether or not the individual has a medical condition that might produce psychological symptoms.

In asking questions about mental-health symptoms, mental-health professionals are often exploring if the individual suffers from hallucinations or delusions, depression and/or manic symptoms, anxiety, substance abuse, as well as some personality disorders (for example, schizotypal personality disorder) and developmental disorders (autism spectrum disorders). Since some of the symptoms of schizophrenia can also occur in other mental illnesses, the mental-health screening is to determine if the individual suffers from schizoaffective disorder or other psychotic disorder, bipolar disorder, an anxiety disorder, or a substance abuse or personality disorder. Any disorder that is associated with bizarre behaviour, mood, or thinking, like borderline personality disorder or another psychotic disorder, as well as dissociative identity disorder (DID), formally known as multiple personality disorder (MPD) may be particularly challenging to distinguish from schizophrenia. In order to
assess the person's current emotional state, health-care providers perform a mental-status examination as well.

1.2.4 Treatment of schizophrenia

Antipsychotics are useful in treating schizophrenia and schizoaffective disorder. The chemical revolution in the treatment of schizophrenia began with the release of chlorpromazine in 1954. Within 8 months of its appearance on the market, the drug had been administered to over 2 million patients (Isacc and Armat, 1990; Kramer, 1993). Chlorpromazine allowed many formerly hospitalized patients to be released to live in community. The introduction of chlorpromazine and other antipsychotics like haloperidol and clozapine improved the treatment of psychosis. The benefits of these drugs for patients are clear: Frightening hallucinations are eliminated or reduced, the patients feel more relaxed and in control, and a return to home and family life is often possible. But there are downsides with all psychotropic drugs as some patient complaint of feeling lethargic and others experience restlessness, muscle rigidity or dystonia. Negative symptoms such as social isolation and flat affect, often remain with these antipsychotics. In addition, these drugs do not offer a cure; patients must continue to take them to maintain benefits. Many patients stop taking the medication after some time resulting in a return of symptoms (Engstrom et al., 1997).

Now a number of antipsychotic drugs are available and they are classified as typical and atypical antipsychotics. Typical Antipsychotics were first developed in the 1950s and act primarily to decrease the level of the neurotransmitter dopamine i.e. antagonists at D2 in the brain. Blocking of D2 receptor causes relative excess cholinergic effect which is the main cause of extrapyramidal side effects. Typical antipsychotics include phenothiazines, butyrophenones (haloperidol, trifluoperidol, droperidol, penfluperidol), thioxanthines (Thiothixene, flupenthixol), other heterocyclics (pimozide, loxapine, reserpine, molindone). Atypical antipsychotics acts on multi-receptors. They are selective monoaminergic antagonists with high affinity for 5-HT2A. Along with it, atypical antipsychotics act on D1 to D4, α, M and H1 receptors. Less affinity to D2 receptors, is responsible for less extrapyramidal side effects. Atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine and ziprasidone.
Effective treatment, although not curative, has made an important difference in the course of the disorder, sharply reducing symptoms and the rate of relapse. Typical and atypical antipsychotics have transformed the lives of many schizophrenics by abolishing troublesome symptoms and permitting return to more normal behaviour. Line of treatment of psychosis is shown in Figure 1.1.
1.2.5 Benefits of atypical over typical antipsychotics

Earlier methods for treating schizophrenia typically involve use of the typical antipsychotic agents viz., haloperidol, clozapine and flumezapine. However these drugs are problematic in a number of ways. Haloperidol causes high incidence of extrapyramidal symptoms e.g. parkinsonism, acute dystonic reactions, akathisia and tardive dystonia while clozapine has been shown to be more effective than other antipsychotics although the possibility of severe side effects like agranulocytosis. Typical antipsychotics suppress only positive symptoms of schizophrenia (Baldessarini and Tarazi, 2001).

Newer atypical antipsychotic drugs such as risperidone and olanzapine have been developed which are highly effective in the treatment of psychosis and are safer than the older drugs. These may be better tolerated and more potent. These drugs have lesser side effects than the typical antipsychotics. These antipsychotics cause extrapyramidal side effects only at higher doses and suppress both negative and positive symptoms (Mortimer and Al Aqib, 2007; Stahl and Grady, 2004).

1.2.6 Challenges of existing dosage forms of atypical antipsychotics

The duration of treatment of these atypical antipsychotic drugs is quite prolonged, therefore, the formulations of newer atypical psychotics that deliver sustained and controlled amount of therapeutic agent is required as they may improve compliance and offer efficacy and safety benefits in long term management of patients (Keith, 2006). The evidence that continued medication is beneficial to chronic schizophrenia patients is now almost universally acceptable (Robinson, 2004; Samanta et al., 2003). There have been reports in the literature that long acting dosage forms of antipsychotic medications are able to improve adherence, delay relapse and lower overall treatment costs. The reason behind is that effective treatment of patients with schizophrenia is often compromised by patient non-adherence followed by relapse that leads to hospitalization which is the largest expenditure for this disease (Wertheimer et al., 2005). Oral route of atypical antipsychotics causes orthostatic hypotension and patient compliance is major problem with conventional formulations. So there is always a requirement of patient friendly delivery system for atypical antipsychotics.
Researchers are exploring new methods of drug administration to improve patient compliance, adherence to medication and delay relapse. Advances in oral drug delivery have come in the form of sustained release formulations of psychotropic drugs, which typically produce lower maximum concentrations and higher trough concentrations, thus reducing side effects and improving tolerability. The future of pharmacologic treatment for psychiatric disorders may be in part dependent on non-oral drug delivery systems such as small pumps that can inject drugs directly into the brain, electrical devices that stimulate discrete brain regions, implants and transdermal delivery systems (Kilts, 2003). These systems have been developed to address suboptimal therapy outcome by enhancing drug delivery, assuring safety of treatment, reducing side effects and improving compliance. In particular, patients with chronic neurological diseases often require multiple administrations of drug during the day to maintain constant plasma medication levels, which in turn increases the likelihood of poor adherence (Lorenzo et al., 2006). In these cases, long acting psychotropic drugs can eliminate the need for multiple dosing (Keith et al., 2006).

1.3. TRANSDERMAL DELIVERY FOR SCHIZOPHRENICS

Drug delivery systems such as patches that are more patient and caregiver – friendly may enable patients to continue treatment for longer periods and to attain greater, more sustained treatment benefits (Oertel et al., 2007). Not all drugs are easily absorbed through the skin but, for those that are or can be altered or enhanced to be so, transdermal delivery offers distinct advantages (Ranade et al., 1991). For schizophrenics, transdermal delivery seems to be good option and it may provide the following advantages:

- Long acting dosage forms improve adherence, delay relapse and lowers overall treatment costs.
- Reduction of frequency of dosing and easy application leading to patient compliance
- Easy termination of medication, if required.
- No first pass effect
- Maintenance of constant and prolonged drug level.
• Less chance of over and under-dosing as a result of pre-programmed drug delivery at a required therapeutic rate
• Lower daily dosage of drug by continuous drug input.

1.3.1 Criteria for selection of drug for transdermal drug delivery

In the present investigation, it is proposed to design and formulate transdermal delivery system for atypical antipsychotics. For transdermal drug delivery, drug should meet following criteria (Costa et al., 1997):

• Drug must be non-ionic
• Low molecular weight (less than 500 Da)
• Adequate solubility in oil and water (log P:1-3)
• Low melting point (less than 200 °C)
• Potent (daily dose less than 100 mg)
• No skin irritation

On this basis, Olanzapine and Risperidone were found to be good candidates for TDDS.

1.3.2 Improved transdermal technologies for psychotropic drugs

The efficacy of transdermal drug delivery may be improved by altering the system to enhance the bioavailability. The main limitation of transdermal drug delivery is the lipoidal barrier of stratum corneum (Sivamani et al., 2007). The barrier properties can be modified by hydration or through the use of chemical penetration enhancers, which improve penetration through lipid disruption, protein interaction or portioning promotion (Banerova et al., 2001). Other modifications include the use of liposomes or vesicles which can be used to entrap drug molecules for easier transport through the lipid bilayer of the stratum corneum (Benson Heather, 2006). A suitable prodrug can be used (Barry, 2001), which is activated after initial penetration. Costa et al., (1997) studied transdermal therapeutic system containing lorazepam, an antianxiety benzodiazepine. To increase the permeation rate of lorazepam, three permeation enhancers’ viz., Tween 80, sodium lauryl sulphate (SLS) and benzalkonium chloride (BC) were used in different concentrations. Results showed the increase in penetration with all permeation enhancers and the best permeation enhancement results were obtained using BC in concentration of 5%. Parikh and Ghosh (2005) investigated the feasibility of transdermal drug delivery of fluoxetine,
an antidepressant, across human cadaver skin using either salt or base form of fluoxetine along with permeation enhancers like azone and ethanol. The study indicated that permeation of fluoxetine free base was significantly enhanced from a vehicle system containing 65% v/v ethanol and the results were promising for developing a TDDS of fluoxetine. Thus psychotropic drugs can be used in transdermal system along with various permeation enhancers so that transdermal delivery of these drugs could be regarded as feasible (Nokodchi et al., 2003; Puglia et al., 2001). 

To expand the number of compounds that can be delivered via the skin, researchers are developing novel transdermal technologies, including iontophoresis which uses an electric current to cause charged particles to move, electroporation involves the creation of aqueous pores in lipid bilayers by the application of a short (microseconds to milliseconds) electric pulse and low frequency sonophoresis, which enhances the transport of permeants, such as drugs through cell membranes as a result of ultrasonic energy (Frost and Sullivan, 2003; Merino et al., 2003; Semalthy et al., 2007; Sharma et al., 2000). With these technologies molecular size, solubility, melting point and dose size is not a limiting factor. Iontophoretic transdermal delivery of haloperidol across pig skin was studied by Alvarez-Figueroa et al., (2006). The results indicated that iontophoresis may be used to improve the topical application of haloperidol for the treatment of chronic psychosis.

Singh et al., (1999) studied transdermal iontophoretic delivery of methylphenidate. This study was undertaken to evaluate the passive and electrically assisted transport (iontophoresis) of methylphenidate from aqueous methylphenidate hydrochloride solutions across excised human skin. It was observed that iontophoresis significantly enhanced protonated methylphenidate transport as compared with passive delivery. Simon et al., (2006) applied a mathematical model of iontophoretic transdermal drug delivery to study the effects of physical parameters on the cumulative amount of amitriptyline HCl collected. The results supported that the increase in the iontophoretic transdermal delivery of some drugs is mainly due to a rise in the surface concentrations of the drug. Iontophoretic transdermal patch of lithium was developed by Nerneroff and Kilts. This method involved the attachment of a dermal patch to the patient, wherein the patch delivered lithium in response to a
current. The device and method of the invention allowed the administration of lithium ion to the bloodstream within therapeutic window without peaks (creating damage of toxicity) and troughs (creating the danger of breakthrough symptoms and decreased patient compliance) experienced with conventional methods of lithium administration (Nerneroff et al., 2002). Clearly the opportunities for transdermal drug delivery have been greatly expanded through application of new formulation technologies (Gordon et al., 2003). Iontophoresis appears to be a promising and perhaps the most efficient assisted delivery technique for future transdermal therapy of psychotropic drugs (Alvarez-Figueroa et al., 2006; Kilts et al., 2003).

Transdermal gels represent an improvement compared with transdermal delivery by patches because they offer more dosage flexibility, less irritation potential and a better cosmetic appearance. Advanced transdermal delivery gel technology was developed in order to provide enhanced passive skin permeation of various active drugs for treatment of anxiety and psychosis (Alberti et al., 2005; Kang et al., 2005; Lim et al., 2006). A list of psychotropic transdermal formulations that are reported in various research publications is shown in Table 4.

The recent transdermal technologies challenge the paradigm that there are only few drug candidates for transdermal drug delivery. With the active transdermal technologies, molecular size, melting point, solubility, dose size is not a limiting factor. The opportunities for transdermal drug delivery are expanding through the application of new formulation technologies and active delivery systems. Now a much wider set of compounds, including macromolecules, can be delivered transdermally at therapeutic levels (Higo, 2007). However, for these novel delivery methods to succeed and compete with those already on the market, the primary issues that require consideration include device design and safety, efficacy, ease of handling and cost effectiveness (Brown et al., 2006). The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of transdermal drug delivery products continue to deliver real therapeutic benefit to patients around the world. While this proven technology still offers significant potential for growth, with many new product offerings in the coming years, next generation drug delivery technologies will enable much broader application of transdermal drug delivery to pharmaceutical industry. The transdermal
drug delivery may eliminate needles for administration of wide variety of drugs in the future utilizing recent evolving technologies.

**1.4. RESEARCH ENVISAGED**

The last years have seen several improvements in the treatment of psychiatric disorders. In particular, many new drugs other than classical neuroleptics are now available for the treatment of schizophrenia. The new drugs, called ‘atypical antipsychotics’ such as risperidone and olanzapine seem to be more effective than the previously used ones, since they can suppress both, positive and negative symptoms of schizophrenia, whereas classical neuroleptics are only active against the positive symptoms of the illness. Furthermore, the recent drugs cause less extrapyramidal side effects than the older ones. On the contrary, today schizophrenia is believed to be a multifactorial disease which can be treated most effectively using drugs which interact with multiple neurotransmitter system.

Risperidone is used for producing an antipsychotic effect or alleviating behavioural disturbances associated with neurodegenerative disorders, such as schizophrenia and bipolar disorder. It is occasionally used to treat severe behavioural disorders in children and teenagers with autistic disorders. Risperidone is taken once or twice per day, by mouth. The dose is in the form of a tablet, a liquid or an orally disintegrating tablet. It has been reported that for producing antipsychotic effect in a patient the daily dose is about 2 to 8 mg; for alleviation of behavioural disturbances associated with neurodegenerative disorders the daily dose is less. It has also been reported that 6 mg daily dose (3 mg *b.i.d.*) is effective to treat psychotic symptoms.

However, it is not easy to deliver an adequate amount of risperidone for effective treatment of neurological disorders such as schizophrenia, particularly sustained delivery over a period of time that is convenient to use, especially for individuals that may need assistance to receive medication orally or via injection. Thus far, there is still no transdermal risperidone delivery system of a convenient size that may be applicable on a patient by him over a period of days and that can deliver a flux adequate for therapeutic effect. The transdermal delivery of this
drug may result in lower adverse effects \((i.e.\) orthostatic hypotension\) than seen with oral delivery. Further, a transdermal patch may allow a more steady sustained delivery than doses taken orally at time intervals hours apart. The transdermal form of drug could allow use in patient population that cannot take oral medication. So there continues to be a need for improved delivery of risperidone, especially sustained delivery over a period of time.

Olanzapine is a novel antagonist of dopamine at the D-1 and D-2 receptors and in addition has antimuscarinic anticholinergic properties and antagonist activity at 5HT-2 receptor sites and at noradrenergic alpha receptors. The drug has relaxant, anxiolytic and anti-emetic properties and is useful in the treatment of psychosis, acute mania and mild anxiety states and is particularly useful in the treatment of schizophrenia. Currently olanzapine is administered orally or by injection. It is usually administered as one or two daily oral doses, for an overall dosage of 5-20 mg per day. The drug has also been introduced in Italian market as film coated, gastro-resistant Zyprexa\textsuperscript{®} tablets containing 5 or 10 mg of olanzapine each. Olanzapine is an extremely effective antipsychotic agent but drug non compliance is a serious problem and it is believed to account for approximately one third of all short stay hospital costs. Transdermal delivery of olanzapine may enhance patient compliance by providing an advance delivery system useful for administering the drug for sustained period of time. There are number of advantages of administering olanzapine transdermally are: gastrointestinal and other side effects associated with oral administration are avoided; continuous delivery provides for sustained blood levels; the transdermal patch is easily removable if any side effect do occur; and the likelihood of patient acceptance is significantly improved.

In general, transdermal delivery of risperidone and olanzapine may decrease side effects that are associated with oral drug delivery. But the successful development of the transdermal therapeutic system depends on a pondered choice of drug. The drug should neither be irritable nor produce allergic reaction when applied in this delivery system. It should permeate the skin in adequate amounts to produce the desired therapeutic effect. The skin is very effective as a selective penetration barrier. Percutaneous absorption
involves the passage of drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. Thus the transport across the skin is a complex phenomenon. It is the cells of stratum corneum which present the primary barrier to absorption of transdermally administered drugs. The stratum corneum is a thin layer of highly keratinized cells approximately 10-15 microns thick over most of the body. It is believed to be high degree of keratinisation within these cells as well as their dense packing which creates in most cases a substantially impermeable barrier to drug penetration. Relatively recent advances in transdermal drug delivery have enabled effective administration of a variety of drug through the skin. These advances include the development of a number of skin penetration enhancing agents or permeation enhancers to increase the skin permeability. Penetration enhancers such as surfactants, vegetable oils are the substances that facilitate the absorption of drug through the skin by temporarily diminishing the impermeability of the skin.

The above mentioned delivery system has not been exploited for atypical antipsychotics till now. As these drugs have an important role to play in the treatment of schizophrenia, it is desired to develop low dose maintenance therapy of these antipsychotics which can minimize the risk of major side effects, help in overall cost savings and address the problems of poor compliance in patients. Based on this hypothesis, it is envisaged to develop transdermal drug delivery system (TDDS) of these antipsychotic drugs that specialises in phasing the drug administration so that the optimum amount of the drug is provided to control the disease condition along with minimum side effects. This will lead to cost effectiveness of healthcare treatment for long term management of the disease.

To increase the permeation rate of drugs through transdermal patches, chemical permeation enhancers like solvents, azones, pyrrolidones and surfactants are generally used. Solvents may cause reversible denaturation of keratin, azones show better permeability but seem to have less effect on human skin, and ionic surfactants may cause skin irritation. Recently, natural products have received increasing attention for use as penetration enhancers due to their better
safety profile. Vegetable oils are fixed oils and used in cosmetics and medicines. They have been found to be effective penetration enhancers due to presence of fatty acids. In some cases fatty acids have been reported to be more effective than terpenes and azone. Vegetable oils are safe to use, metabolized in the body and are easily available (Charu et al., 2005). Thus various permeation enhancers belonging to the group of surfactants (BC, SLS, span 20) and vegetable oils (olive oil, jojoba oil and groundnut oil) will also be compared to find out their effect on the rate of permeation of drug.