Chapter 1

CHAPTER-1: A Review on Antipsychotic Drug Substances and Importance of Alternate Synthetic Approaches to Drug Substances for Pharmaceutical Industry:

PART-1: Review on Antipsychotic Drug Substances

1.1.1: Introduction

Drug substances, often referred as Active Pharmaceutical Ingredients are used seldom in preparing composition of a medicine for curing, alleviating or preventing a disease or disorder, and have an indispensable role in the day to day life of human. Today, we cannot even imagine our lives without drug substances (APIs) and hence the diverse era of:

- drugs for pain,
- drugs for allergies,
- drugs for cancer,
- drugs for AIDS and
- drugs for mental health or the like.

Drugs that have been designed rationally and subsequently synthesized in the industries or purified from nature, from fermentation process, or via bioengineered pathway, however all drug compounds are usually clinically tested before their approval by the Drug Authorities.

In the 19th century, medicines were concocted with a mixture of empiricism and prayer. Trial and error inherited lore or mystical theories
were the basis of world’s pharmacopoeias. At the end of the century, a very less number of therapeutically effective substances were widely treated as medicines. Almost by accident a few authentic drugs such as quinine\(^1\), digitalis\(^2\), cocaine\(^3\) etc., were developed based on the wisdom and herbal lore of the past. The century ended with the development of the first two synthesized drugs antipyrine and aspirin\(^4\), which represent the triumph of chemistry over folklore and technology over cookery.

From these scattered seeds of therapeutic foundation, drug technology experienced remarkable growth in the first two decades of the 20\(^{th}\) century, a period that can be associated to a weedy flowering of quackery and patent medicines twining about a hardening strand of authentic science and institutions to protect and nourish it. With the advent of new analytical techniques, automation, genetic engineering, computers, immunology, genomics, biotechnology explosive growth in the field of drugs and pharmaceuticals was encountered. While chemoinformatics and bio-informatics underpin research at a scientific level, rapid communication between individual researchers across continents now allows the global exchange of ideas, tools and technologies.

The exchange of ideas among one another facilitated the development of new technologies and increases the competitive behavior. New knowledge and occasional serendipity led to new drugs, with the passing by years many new drugs or therapeutically useful compounds have been developed, making chemotherapy an important part of
medical practice. In the mean time, many antibiotics, vaccines, cardiovascular drugs, anti-hypertensives, anti-coagulants, anti-inflammatory drugs, relaxants, stimulants, depressants, antipsychotics, analgesics, narcotics, barbiturates, vitamins and dietary minerals have been developed and are still on the way of development for improved therapeutic efficacy.

1.1.2: Antipsychotic definition and its role in therapy

The meaning of "psyche" is mind or soul, and word "-osis" corresponds to abnormal condition in Greek. Hence, psychotic is often described as involving a "loss of contact with reality." Stedman's medical dictionary defines psychosis as "a severe mental disorder, which is characterized by de-arrangement of loss of contact and personality with reality and causing worsening of normal social functioning". The possible causes for psychosis may be the result of an underlying mental illness such as bipolar disorder or Schizophrenia. The cause for psychotic diseases may also be based on severe mental stress.

People experiencing a psychotic episode may exhibit personality changes and disorganized thinking. Later, it results lack of insight into the unusual nature of their behaviour, impairment in carrying out the daily activities and will become difficulty with social interaction.

However, at some point of time most people have unusual and reality-distorting experiences and some have even found inspiration or
Chapter 1

religious revelation in them. As a result, it is arguable that psychosis is not fundamentally separate from normal consciousness, but rather, is on a range with normal consciousness. In this view, people who are clinically found to be suffering from psychotic diseases may simply be having particularly intense or distressing experiences and incidents.

Psychosis is explained in terms of neurotransmitter dopamine. It is assumed that the dopamine of psychosis has been influential and states that psychosis results from an over activity of dopamine function in the brain, in particular the mesolimbic pathway. There exists a complex relationship in between dopamine and psychosis. The dopamine receptor D\textsubscript{2} suppresses and D\textsubscript{1} receptor increases adenylate cyclase activity. The blocked dopamine spills over to the D\textsubscript{1} receptors during the administration of D\textsubscript{2} blocking drugs. The increased adenylate cyclase activity affects genetic expression in the nerve cell; usually this process takes certain time period. Hence, antipsychotic drugs take a week or two to reduce the symptoms of psychosis.

Moreover, newer and equally effective antipsychotic drugs actually block slightly less dopamine in the brain than older drugs whilst also blocking 5-HT\textsubscript{2}A receptors, suggesting the “dopamine hypothesis” may be oversimplified.

The antipsychotic drugs are also termed as neuroleptic drugs, or neuroleptics, which is derived from Greek in which *neuro* refers to the
nerves and *lept* means "to take hold of". Thus the word neuroleptic means "taking hold of one's nerves".

1.1.3: **Antipsychotics - History**

The first antipsychotic drug Chlorpromazine\(^\text{10}\) (1) was developed as a surgical anesthetic. Due to its calming effect nature, this drug was used on psychotic patients. Apart from this, it also causes a reduction of psychosis unrelated to the sedating effect. The drug hailed as a "cure" for schizophrenia, when lobotomy was a common treatment for psychosis.

Antipsychotics are divided into two categories. The first category is called as typical antipsychotics and also referred to as first generation antipsychotics or classical neuroleptics or major tranquilizers or conventional antipsychotics. In the year 1950s, these drugs were used to treat psychosis in particular, schizophrenia.

Second category drugs, known as atypical antipsychotics or second generation antipsychotics, are used to treat psychiatric conditions. Atypical antipsychotics are approved for use in the treatment of psychotic agitation, schizophrenia, mania, bipolar maintenance and other indications. Atypical antipsychotic drugs work differently from typical antipsychotic drugs.

It has become important to examine the mechanism of action of atypical antipsychotics and how it differs from that of the more typical
antipsychotics. The older traditional antipsychotics or typical antipsychotics bind more tightly than dopamine itself to the dopamine D$_2$ receptor, with dissociation constants that are lower than that for dopamine. The newer, atypical antipsychotics bind more loosely than dopamine to the dopamine D$_2$ receptor and have dissociation constants higher than that for dopamine. These tight and loose binding data agree with the rates of antipsychotic dissociation from the human-cloned D$_2$ receptor.

1.1.4: Typical antipsychotics

Chlorpromazine (1) is having phenothiazine moiety and typical antipsychotic for low to middle potency neuroleptics. Chlorpromazine was marketed under the trade names of “Largactil” and “Thorazine” to become the first medication as an antipsychotic in between 1950s and 1960s. Over 100 million people were treated with this drug, from late 1960s its use has fallen down rapidly due to its severe extrapyramidal side effects and tardive dyskinesia. The anticholinergic properties of chlorpromazine results extrapyramidal side effects, which include sedation, lowering of seizure threshold, dry mouth, constipation and urinary retention.
Acetophenazine\textsuperscript{11} (2) is also known as Phenothiazine, is an antipsychotic drug of moderate potency and is useful in the treatment of false perceptions such as hallucinations or delusions, disorganized and psychotic thinking.

Haloperidol\textsuperscript{12} (3) belongs to butyrophenone antipsychotic drug category and is having similar pharmacological effects to that of Phenothiazine. The potency of Haloperidol is much higher than Chlorpromazine, which is approximately 50 times on a weight basis. The drug was used to treat acute psychotic states such as acute schizophrenia and delirium. It is classified as highly potent neuroleptic due to its strong central anti-dopaminergic action and is noted for early and late extrapyramidal side-effects. The use of Haloperidol in long-term treatment may results severe depression which leads to suicidal thinking. However, such risks may be minimized with the help of changing to mildly potent neuroleptic drugs in combination with appropriate antidepressants.
Droperidol\textsuperscript{13} (4) chemically belonging to butyrophenone family, is an anti-dopaminergic drug used as antipsychotic and an anti-emetic. It is a potent D\textsubscript{2} (dopamine receptor) antagonist with some histamine and serotonin antagonist activity. It has been used as an antipsychotic in doses as high as 10mg.

Perphenazine\textsuperscript{14} (5) is a typical antipsychotic drug and belonging to piperazinyl Phenothiazine group. It is considered as a high potent having 10 to 15 times more potency than Chlorpromazine. The frequency and severity of early and late extrapyramidal side-effects of this drug is almost same to that of Haloperidol in equal doses. It is particularly useful for the treatment of agitated psychotic patients. Perphenazine may be used to treat patients who are with life-threatening (febrile) catatonia, a state in which the patient is extremely agitated, but is not able to express the views by him/herself independently. In this situation Perphenazine may be used together with electroconvulsive therapy and correction of electrolytes/fluids in the body.
Prochlorperazine\textsuperscript{15} (6) mainly used for the treatment of psychosis and the manic phase of bipolar disorder is another piperazinyl Phenothiazine class of antipsychotic agent having highly potent neuroleptic activity. It is about 10 to 20 times more potent than Chlorpromazine. The incidence and severity of extrapyramidal side effects are quite similar to that of Haloperidol in the long term treatment.

Fluphenazine\textsuperscript{16} (7) also belongs to the piperazinyl Phenothiazine class and the potency is around fifty to seventy times more than Chlorpromazine. Its main use is as a long acting injection given once every two or three weeks to people who are suffering with schizophrenia and who have a poor compliance with medication resulting frequent relapses of illness.

Trifluoperazine\textsuperscript{17} (8) is another typical antipsychotic drug of the Phenothiazine group and is primarily indicated for the treatment of schizophrenia. The usage of drug rapidly declined due to its highly
frequent and severe, early and late tardive dyskinesia, which is a type of extrapyramidal symptom.

Thioridazine\textsuperscript{18} (9) is a piperidine antipsychotic drug. It was used in the treatment of schizophrenia and psychosis widely in olden days. However, the recent reports indicate that the use of this drug is having certain side effects at high doses such as cardiotoxicity and retinopathy. A serious side effect is the potentially fatal neuroleptic malignant syndrome. It exerts its actions through a central adrenergic-blocking, a dopamine-blocking and minor anticholinergic blocking activity.

Mesoridazine\textsuperscript{19} (10) is a metabolite of Thioridazine, is also used in the treatment of schizophrenia, alcoholism, organic brain disorders, and psychoneuroses. It is having serious side effects, which include akathisia, tardive dyskinesia and the potentially fatal neuroleptic malignant syndrome. It exerts part of its actions through depression of hypothalamic centers, having the similar properties with other Phenothiazine drugs.

Sulforidazine\textsuperscript{20} (11) is a typical antipsychotic and a metabolite of Thioridazine. Mesoridazine is more potent than the parent compound
Chapter 1

i.e., Thioridazine, whose pharmacological effects are believed to be largely due to its metabolism into Sulforidazine and Mesoridazine.

Promazine\textsuperscript{21} (12) is an older medication used to treat schizophrenia. The atypical antipsychotics such as Olanzapine and Quetiapine have been replaced the use of Promazine for the treatment of antipsychotic diseases. It has predominantly anti-cholinergic side effects, though extrapyramidal side effects are negligible.

Triflupromazine\textsuperscript{22} (13) is typical antipsychotic medication of the Phenothiazine class. The possible serious side effects include akathisia and tardive dyskinesia, as well as the rare, but potentially fatal, neuroleptic malignant syndrome.

Levomepromazine\textsuperscript{23} (14) is an aliphatic Phenothiazine neuroleptic drug. It has a low antipsychotic potency (approximately half as potent as chlorpromazine) and is used for the treatment of psychosis, particularly schizophrenia, manic phases of bipolar disorder. It should never be used in the treatment of agitated depressions because this drug increases agitation through the side effect of akathisia. Patient
willingness to take this drug is low because of agonizing the side effect of akathisia.

Chlorprothixene\textsuperscript{24} (15) is categorized as thioxanthene class of typical antipsychotic drugs. It has approximately half to 2/3 antipsychotic potency with respect to Chlorpromazine. This drug was introduced in 1959 into the global market and hence is a first generation antipsychotic drug with 45+ years of clinical evidence. Its principal indications are the treatment of psychotic disorders and of acute mania occurring as part of bipolar disorders. Sometimes, it is prescribed during pre and post-operative states with anxiety and insomnia or severe nausea and emesis.

Flupenthixol\textsuperscript{25} (16) is a typical antipsychotic neuroleptic drug. It has a thioxanthene moiety and hence categorized as Phenothiazine derivatives. It is mainly used for the treatment of schizophrenia with the dosage of two or three times per week as a long acting injection to the people who have a poor compliance with oral medication and suffer frequent relapses of illness. Flupenthixol acts by antagonism of D\textsubscript{1} and
D_{2} dopamine receptors. The side effects are similar to many other typical antipsychotics with low anti-cholinergic adverse effects.

Thiothixene\textsuperscript{26} (17) was widely used for the treatment of schizophrenia for few decades in olden days. It is a thioxanthene derivative and is the cis isomer of \( N, N\)-dimethyl-9-[3-(4-methyl-1-piperazinyl)-propylidene] thioxanthene-2-sulfonamide. It is rarely used today and is replaced with Risperidone, an atypical antipsychotic drug.

Zuclopenthixol\textsuperscript{27} (18) is having thioxanthene moiety and belongs to typical antipsychotic neuroleptic drug. The approved dosage form of drug as a long acting intramuscular injection for treating the patients who suffers from schizophrenia. It is further used as a shorter intramuscular injection in the acute sedation of psychotic in-patients. It mainly acts by antagonism of D\textsubscript{1} and D\textsubscript{2} dopamine receptors apart from its anti-histamine activity.

Pimozide\textsuperscript{28} (19) is a typical antipsychotic drug having high potency compared to Chlorpromazine and even more potent than Haloperidol on weight basis. Pimozide has been used for ADHD (Attention Deficit
Hyperactivity Disorder) in children and adolescents. It has been further used in the treatment of delusional disorder. This drug is typically prescribed as a last resort, when the patient has failed to respond to other medications because of its severe side effects. The side effects include akathisia, tardive dyskinesia, neuroleptic malignant syndrome and long QT syndrome.

1.1.5: Atypical antipsychotics

The atypical antipsychotic drugs are having fewer side effects with additional benefits for the 'negative symptoms' of schizophrenia; hence these are preferred as a first line treatment for many psychotic related diseases.

Clozapine\textsuperscript{29} (20) was the first of its kind in the group of atypical antipsychotics and was approved for the treatment of resistant schizophrenia and for reducing the risk of suicidal behaviour by the United States Food and Drug Administration (USFDA). It has shown superior in efficacy in treating schizophrenia than the older typical antipsychotics who have responded poorly to other medication. The
common side effects are anti-cholinergic in nature, sedation, constipation and dry mouth. This drug has not been widely used in the global market though the relapse rate is lower and patient acceptability is better than other drugs.

Risperidone\textsuperscript{30} (\textbf{21}) is an atypical antipsychotic medication approved by the USFDA in 1993 for the treatment of schizophrenia. The molecular structure of Risperidone constructs with benzisoxazole and piperidine fragments. This is the only drug approved for treatment of schizophrenia and bipolar disorder in children with the age group of 13 to 18 years. The bipolar disorder associated with manic states, irritability with autism in children and adults may also be treated for the short-term by prescribing Risperidone as a medicament. Some instances, it has also been used "off-label" for the treatment of anxiety disorders, such as obsessive-compulsive disorder. The common side effects during the therapy include anxiety, insomnia, low blood pressure, muscle pain, sedation, increased salivation, and stuffy nose.
Amisulpride\textsuperscript{31} (22) is an atypical antipsychotic drug and is a selective dopamine antagonist. It has a high affinity for D\textsubscript{2} and D\textsubscript{3} dopaminergic receptors but it is not approved by the USFDA. However, it is used in Europe and Australia to treat psychosis and schizophrenia. The recent study concludes that Amisulpride is an appropriate first-line treatment for the management of acute psychosis.

Quetiapine\textsuperscript{32} (23) is an oral atypical antipsychotic drug used for treating schizophrenia and bipolar disorder either alone or in combination with other drugs. Quetiapine is approved in multiple dosage forms and administered 2-3 times daily. Quetiapine assumed to be inhibits communication between nerves of the brain and functions since its exact mechanism is unknown. It’s unique property is blocking receptors on the nerves for several neurotransmitters and beneficial effect is due to blocking of the dopamine type 2 (D\textsubscript{2}) and serotonin type 2 (5-HT\textsubscript{2}) receptors.
Ziprasidone\textsuperscript{33} \((24)\) is another prominent atypical antipsychotic approved in the year 2001 by the USFDA. Ziprasidone is approved in the form of hydrochloride salt as oral tablets for the treatment of schizophrenia. The intramuscular injection form containing Ziprasidone mesylate as an active ingredient is approved for the acute agitation in schizophrenic patients. Ziprasidone has got an approval for the treatment of acute bipolar disorder associated with mania as second method of indication.

Paliperidone\textsuperscript{34} \((25)\) is an atypical antipsychotic and approved in the year 2006 for the acute treatment of schizophrenia in the form of an extended release formulation with once-daily dosing. It is a primary active metabolite of the older atypical antipsychotic Risperidone. Its therapeutic effect may be due to a combination of D\textsubscript{2} and 5-HT\textsubscript{2A}
Chapter 1

receptor antagonism. The drug significantly reduces side-effects present in other antipsychotic drugs formerly used to treat schizophrenia and bipolar disorder.

Olanzapine\textsuperscript{35} (26) is classified as a thienobenzodiazepine though it is structurally similar to Clozapine which belong to the dibenzodiazepine drugs. Olanzapine has a higher affinity for 5-HT\textsubscript{2} serotonin receptors than D\textsubscript{2} dopamine receptors. It has a lower affinity for histamine, cholinergic, muscarinic and alpha adrenergic receptors like other atypical antipsychotics. It has certain sedating properties because of weak affinity for benzodiazepine receptors. This drug may involve antagonism at serotonin receptors resulting antipsychotic activity. The antagonism of dopamine receptors is associated with extrapyramidal side effects along with therapeutic effects.
Chapter 1

Aripiprazole\textsuperscript{36} (27) was approved for the treatment of schizophrenia and is the sixth atypical antipsychotic medication of its kind. Aripiprazole has been approved by the FDA for the treatment of acute manic and mixed episodes in both pediatric and adult patients. The mechanism of action of Aripiprazole is different from the other FDA-approved atypical antipsychotics such as Clozapine, Olanzapine, Quetiapine, Ziprasidone, and Risperidone. It appears that Aripiprazole is a D\textsubscript{2} partial agonist and selective agonist rather than antagonizing the D\textsubscript{2} receptor. It is also a partial agonist at the 5-HT\textsubscript{1A} receptor whereas other drugs of the same category display an antagonist profile at the 5-HT\textsubscript{2A} receptor. Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors but it has moderate affinity for histamine and α-adrenergic receptors for the serotonin transporter.

PART-2: Importance of Alternate Synthetic Approaches to Drug Substances for Pharmaceutical Industry

1.2.1: Introduction

It has become essential than before to have a sustainable growth to a pharmaceutical manufacturing sector: namely, its public image, its setbacks, and also its opportunities for the coming decades. There have always been available many challenges in developing new drugs or synthesizing the existing drugs in cheapest methods, but these are in
general may be handled by continuous focused research to meet the desired cost.

It is simple to bring out the areas of concerns of process R&D\textsuperscript{37-38} (PR&D) for becoming a prime responsible to lead the various geographies with the required benefits. For example, a new drug will be rarely affected by a procedure whose main responsibility is to design a viable and workable chemical processes. There is, however, it is the only explicit parameter that discloses the role of PR&D is to provide cost-effective Active Pharmaceutical Ingredient (API) or drug substance that will make to the final formulated (drug) product. The API that is to be used to prepare a finished medicine should have relatively high attention with respect to cost of goods such as reagents and solvents. In a more difficult competitive market, developing the cost-effective API has gained its validity and has become essential to sustain in the market. Nowadays, the highest priorities of pharmaceutical industries would be to meet the assigned targets for identifying the best possible route in a given time limit.

It seems there are at least two aspects that are put under strong pressure to the pharma industry, one is low productivity and the second one is enormous competitive cost pressure to reduce the prices to an affordable level. For Process R&D scientists, a technically oriented skills ranging from small scale laboratory work to commercial manufacturing scale is mandatory by focusing on certain key areas like quick process
scale-up to enable fast API delivery with cost consciousness within the projected timelines. The responsibility of designing real process and its understanding at a level to reach the best synthetic route that ultimately to be delivered to the production units lies with the process R&D chemist.

In addition to addressing all of these issues, it is necessary to apply and eventually even to develop, better scientific and technical tools and methods by which tomorrow’s problems can be successfully resolved under the projected future working climate. This will inevitably have to involve more directed and systematically planned approaches, in which the level of predictability will decide their utility on a case-to-case basis.

A prominent feature in the field of synthetic organic chemistry is the reaction pathway selectivity because this means to reduce or completely avoid the formation of side products that might require sophisticated work-up procedures for elimination. Thus, in order to scope with increasingly complex molecular architectures in the future, novel transformations and new reactivity need to be explored and incorporated into the arsenal of methods. The improved atom efficiency that makes efficient use of most of the atomic content in a building block or starting material when transforming it to a product, processes operating along these lines will stand much greater chances of meeting
increasingly tough demands from both environmental viewpoints and a cost perspective.

1.2.2: Related substances or Impurities

Related substance or an impurity is known as any other unwanted material, apart from drug substance and ingredients, which forms either during the synthesis of bulk drug, formulation, or upon storage of both. The safety of a drug product is not only dependent on the toxicological properties of the active drug substance (or API), but also on the impurities that were formed during the various chemical transformations. Therefore, identification, quantification, and control of impurities in the drug substance and drug product are an important part of drug development to get the marketing approvals.

The presence of undesired chemicals as impurities even in small amount may become the cause for the safety profile. Various Pharmacopoeias, such as the British Pharmacopoeia (BP), United States Pharmacopoeia (USP), and Indian Pharmacopoeia (IP) have incorporated limits to certain levels of impurities present in the API's or formulations. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also published guidelines for validation of methods for analyzing impurities in new drug substances. Mainly, the source of impurities will depend on synthetic route of an API, reaction conditions, and purity
Chapter 1

of the starting materials, reagents, solvents, excipients, packaging, and storage of the end product. The following are major categories of impurities as per ICH guidelines.

1.2.2.1: Impurities generated through Organic Substances

The unreacted starting material, by products and degradation products belongs to this category. Based on ICH guidelines, any unknown impurity below 0.1% level by HPLC may not be considered for the identification. However, if the percentage of impurity would be more than 0.1%, it is required to study the toxicology of the impurity to prove the efficacy of a drug product or substance.

1.2.2.2: Impurities generated through Inorganic Substances

Metals that were used as a catalyst during synthesis of a drug substance may be evaluated for their potential risk to human health. There are mainly three categories of metals are described along with their maximum allowable limit in the drug substance or product. Metals such as Platinum, Palladium, Rhodium, Ruthenium and Osmium are belonging to Class 1A/1B and their allowable limit is not more than 10 ppm. The limit of Chromium, Molybdenum and Nickel which are belongs to Class 1C is upto 30 ppm. Copper and Magnesium are categorized as Class 2 metals and the limit would be 250 ppm. The third category limit is 1300 ppm for the metals like Iron and Zinc.
1.2.2.3: Residual Solvents as impurities

The inorganic or organic liquids that are used for the synthesis of the drug substance or the manufacture of the drug product are termed as Solvents. In general, some solvents are known to be toxic in nature; hence certain appropriate limits for these solvents are provided by regulatory authorities. There are mainly four types of solvents as per ICH guidelines. Particularly, Class 1 solvents such as Benzene, Carbon tetrachloride should be avoided during the synthesis. The use of Class 2 solvents such as Acetonitrile, Chloroform, Dichloromethane and methanol are allowed to use with specific limits in the final drug substance or product. The remaining general solvents are categorized as Class 3 and Class 4 solvents whose allowable upper limit is 5000 ppm. It is essential to maintain the limit of solvents based on their class in drug substance for getting marketing approval by regulatory bodies.

1.3: Conclusions

Keeping in view, therapeutic agents (APIs) as antipsychotics plays an important role in day to day human life that to atypical antipsychotics plays major role with respect to therapeutic activity when compared to older generation typical antipsychotics. Among the atypical antipsychotics, Quetiapine, Olanzapine, Ziprasidone and Aripiprazole are having specific importance as medicaments. Hence, the proposed research work was carried out extensively on exploring new probable
Chapters 1

synthetic approaches to selectively atypical antipsychotic - active pharmaceutical ingredients (APIs). Also, in our further endeavor, we attempted to identify, characterize and synthesize the potential related compounds formed during the synthesis of these drug substances.