CHAPTER-1

A REVIEW ON DRUG SUBSTANCES AND IMPORTANCE OF ALTERNATE SYNTHESIS FOR DRUG SUBSTANCES IN PHARMACEUTICAL INDUSTRY
CHAPTER-1: A Review on Drug Substances and Importance of Alternate synthesis for Drug Substances in Pharmaceutical industry.

PART-1: A Review on Drug Substances

1.1.1: Introduction

Heterocyclic compounds are broadly defined as organic compounds which contain carbon ring along with atleast one hetero atom. They are aromatic or non-aromatic in nature and have many applications in medicine, life sciences and agriculture. Based on their importance they are considered as one of the prime interests in biotechnology and pharmaceutical industries.

Active heterocyclic compounds which are treated as drug substances play an important role in pharmaceutical industry. They include nucleic acid, pigments, vitamins and antibiotics. Synthetic heterocyclics are useful as drugs, pesticides, dyes and plastics. Some synthetic drugs include metronidazole, methotrexate, captopril, diazepam and Ibuprofen. Heterocyclic compounds are key building blocks used to develop compound of biological or medicinal interest. Number of pharmaceutical biologically active compounds are derived from heterocyclic compounds which are proven to be broadly economical and useful as therapeutic agents. The challenge for an organic chemist lies in providing a cost effective and affordable medicine to the society. Pharmaceutical process
chemistry is methodology in designing alternate synthesis for active pharmaceutical compounds in a scalable and at affordable cost.

1.1.2: Role of drugs in therapy

Medicines are used to cure diseases. In pharmacology, the medicine we use to treat disease is derived as drug product and the active ingredient present in the drug is referred as drug substance. Drug substances are used in preparing composition of a medicine for curing, alleviating or preventing a disease or disorder, and play a vital role in human life. In formulation the active ingredient will be mixed with excipients to make a capsule, cream or liquid which will be consumed through a particular route of administration which include Oral, Sublingual, Inhalation, Injection and tropical.

Generally, drugs are dispensed into the market in 3 different ways. The drugs that are readily available without any restriction in market are categorized as Over the counter drugs. Drugs which are prescribed by a licensed medical practitioner comes under the category of Prescription only medicine and drugs that are only to be sold by pharmacist are categorized as behind the counter medications.

To get market exclusivity Pharmaceutical companies protect their inventions through patents. Drugs which are not protected by patents (or with expired patents) are called generic drugs.
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Few substances were used as medicines during the end of 19th century. Some authentic drugs which include cocaine\(^7\) quinine\(^8\), digitalis\(^9\), etc., were developed. Development of antipyrine and aspirin\(^{10}\) lead to a major breakthrough in chemistry.

Research is under way to improve the therapeutic efficacy of drugs. Many new drugs of different therapeutic category were developed which includes anti histamines, anti asthmatics, antipsychotics\(^{11}\), antibiotics\(^{12}\), vaccines\(^{13}\), anti-hypertensives\(^{14}\), and cardiovascular drugs.

1.1.3: Drugs - definition

Drug is originated from Old French "drogue", possibly deriving later into "droge-vate" from Middle Dutch meaning "dry barrels", referring to medicinal plants preserved in them. Broadly speaking a drug is any substance, when consumed cures a disease or which enhances mental well being.

1.1.4: Drugs - History

In ancient days people used plants and plant substances to treat all kind of diseases. Later, medicinal creams and pills were employed as treatments. In 1920s, aspirin, codeine and morpholine were used for pain, and quinine for heart disorder. In 1930s, insulin and penicillin became mass manufactured. Legislation was enacted to distinguish prescription and non-prescription drugs and approve drugs through
proper testing and labeling. In 1950s, some new drugs emerged which include antihistamines, corticosteroids, xanthines and antipsychotics. Understanding of human biology and sophisticated manufacturing techniques, development of systematic scientific approaches are the features during this period. Numerous new drugs developed which include Chlorpromazine, Haloperidol which are mass produced and marketed. In 1960, Valium was discovered which became most prescribed drug in history. In 1970s lot of research was done on cancer drugs. Legislation was enacted for strong protection of product and process patents in most of the countries. In 1980s fast approval process for drugs of heart disease and for AIDS is a biggest challenge to regulatory bodies. In 1990s the pharmaceutical industry confronted a new business climate and new regulations, born in part from dealing with world market forces and protest by activists in developing countries. The new antidepressants notably Fluoxetine rapidly became best selling drug.

1.1.5: Drugs – classification and types of medications

Drugs can be classified based on different therapeutic category which includes Antipyretics, Analgesics, Antimalarial drugs, Antibiotics, Antiseptics, cardiovascular, ophthalmology, anti-histamines, anti asthmatics, anti depressants, anti psychotics, anti fungals, anti
hypertensives, anti ulceratives, oncology drugs, male erectile dysfunction drugs, anti diabetic, anti-HIV drugs, anti convulsants etc.

Based on the therapeutic importance to mankind and also to the researchers who have been actively involved in the synthesis, a detailed study on the drug substances related to the following therapeutic category are selected and which is also the basis for our research work.

1. Anti-asthmatics
2. Male erectile dysfunction
3. Antipsychotics
4. Anti-histaminics

1.1.5.1: Anti asthmatics:

Asthma is a chronic disease which causes shortness of breath, narrowing of the airways, and wheezing. Timely medical support can save attacks from asthma. It is a common disease found in all countries and the number of cases increased tremendously over the last three decades. Currently the ratio of affected people from this disease is more in children than in adults.

Asthma attacks can be treated with short acting drugs. In addition, long-term maintenance treatment can prevent attacks from developing. The basis for drug treatment is to reduce the frequency and severity of asthma attacks.
Anti-asthmatic drugs are used for the treatment of asthma. They may be useful either in prevention or treatment of asthma attacks. Basically, asthmatic drugs fall under two distinct categories namely quick-relief drugs and controller drugs. Drugs that fall under quick relief drugs are called Bronchodilators, Corticosteroids and leukotriene antagonists are used as controller drugs which help prevent attacks. The most important drugs in the group of antiasthmatics include Salbutamol\(^1\), Salmeterol\(^2\), Formoterol\(^3\), Montelukast\(^4\), Zafirlukast\(^5\), Pranlukast\(^6\), Zileuton\(^7\), Nedocromil\(^8\).

The classification of antiasthmatics and structures of some of the important drugs belonging to this category are shown below:

\textit{a) Bronchodilators}

![Structure of Salbutamol](image1)

![Structure of Salmeterol](image2)

![Structure of Formoterol](image3)
b) *Leukotriene antagonists*

![Chemical structures of Leukotriene antagonists](image)

Among the above described antiasthmatics, Montelukast has much importance based on the commercial value which prompted us to select this product and is the basis for the present study.

c) *Leukotriene pathway inhibitors*

![Chemical structure of Leukotriene pathway inhibitors](image)

d) *Mast cell stabilizers*

![Chemical structure of Mast cell stabilizers](image)
Montelukast (4) is an oral antiasthmatic drug used for treating asthma and to relieve symptoms of seasonal allergies. Montelukast is approved in multiple dosage of 4mg, 5mg and 10mg. Montelukast comes under the category of leukotriene antagonists.

1.1.5.2: Male erectile dysfunction

Erectile dysfunction is inability to achieve or sustain an erection during sexual performance. During sexual arousal, blood enters and being retained in sponge like bodies within the penis, which develop an erection of penis. Some known causes for erectile dysfunction are neurological problems, hormone deficiencies, cardiovascular diseases, psychological disorders, diabetes, drug side effects and narrowing of blood vessels to penis.

The oral medication has proved effective, as the drug relaxes the muscles of the penis and the walls of the arteries that supply blood to the penis. As a result, more blood flows into the penis and an erection can more easily occur when the penis is stimulated.

The important drugs in this group include Sildenafil (9), Tadalafil (10), and Vardenafil (11).

Sildenafil23 is an oral drug approved by USFDA in 1998 for the treatment of male erectile dysfunction. It is very familiar as Viagra. It is approved
and used in the dosage of 25mg, 50mg and 100mg. It relaxes muscles of the penis and the walls of arteries that supply blood to the penis.

Tadalafil is an oral drug and belongs to a class of PDE5 inhibitor. The drug was approved by USFDA in 2003 for the treatment of male erectile dysfunction. The drug was approved in multiple doses of 5 mg, 10 mg, and 20 mg. It is the third erectile dysfunction drug pill for sale after Sildenafil and Vardenafil. Tadalafil was also approved for the treatment of pulmonary arterial hypertension in the year 2009. The mode of action is similar to Sildenafil.

Vardenafil also belongs to class of PDE5 inhibitor and used for treating erectile dysfunction and sold under the trade name Levitra. It was
approved in multiple doses and available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Vardenafil was proved to be effective in the treatment of premature ejaculation, where it may significantly increase the time from vaginal penetration to ejaculation.

1.1.5.3: Anti psychotics:

Antipsychotic drugs are used to treat schizophrenia and other psychiatric disorders. They are used to control symptoms such as hallucinations, manic-depressive disorder, and disturbed thoughts in schizophrenia. They block the action of neurotransmitter dopamine, also the action of serotonin and other chemicals involved in regulating mood. The side effects include blurry vision, dizziness due to lowering of blood pressure and dry mouth.

The most important drugs in this group include Clozapine\textsuperscript{26}(12), Asenapine\textsuperscript{27}(13), Zotepine\textsuperscript{28}(14), Iloperidone\textsuperscript{29}(15), and Sertindole (16).

Sertindole\textsuperscript{30} is a atypical antipsychotic drug which belongs to class of phenyl indole derivatives developed by Lundbeck a Danish
pharmaceutical company. It is used to treat schizophrenia. It affects dopamine D₂, serotonin 5-HT₂ and α₁-adrenergic receptor. It is not associated with sedative effects.

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1.1.5.4: Anti histaminics:
Anti histamines are drugs that block the effects of histamine, a chemical released during allergic reactions. They are used mainly to prevent or relieve symptoms of allergies such as hay fever and to treat allergic rashes. They are often used in cough remedies, cold and flu remedies and reduces the irritation that causes cough. They are administered orally, as nasal drops, eye drops or skin lotions. The common side effects include drowsiness.

The most important drugs in this group include Clemastine\textsuperscript{31}(17), Desloratadine\textsuperscript{32}(18), Dexchloropheniramine\textsuperscript{33}(19), Diphenhydramine\textsuperscript{34}(20), Fexofenadine\textsuperscript{35}(21), Levocetirizine\textsuperscript{22}, Loratadine\textsuperscript{36}(23).

Levocetirizine\textsuperscript{37} is an antihistaminic drug approved by USFDA in 2007 under the brand name Xyzal with an approved oral daily dose of 5mg. It is the third generation non-sedative anti histaminic drug and works by blocking histamine receptors.
PART-2: Importance of Alternate synthesis for Drug Substances in Pharmaceutical Industry

1.2.1: Introduction

The Pharmaceutical industry is one of the most profitable industry in the technological front. It deals with drugs which are used for human consumption. Due to huge business value, the industry is becoming competitive and the cost involved in launching a new drug successfully into the market is always challenging. Huge investments in research and development by innovator companies in terms of value and resources to bring a new drug into the market involves intensive research. On an average the time consumed in bringing a new drug into the market is 8-12yrs. Based on the efforts made by the innovator companies in successfully launching a drug, the innovator companies were given exclusive rights for 5 yrs to sell the product worldwide. Owing to enormous cost incurred in drug development, innovator companies sell the products at a very high price which is not affordable for a common man.

This brings an opportunity for the generic companies to develop new drugs or synthesizing the existing drugs at low cost, which can be achieved by continuous focused research. The demand for low cost
generic drugs is increasing worldwide, as a result generic competition is increased over the last few decades.

To meet these challenges there is a need for the industry to focus on process research and development by improving the scientific skills and get breakthrough in technologies which in turn reduce the price of drugs substantially to help the common man. To sustain in the market it is mandatory to develop cost effective processes.

There is a need for the industry to develop cost effective alternate synthetic routes which meets the above challenges keeping in view of patent protections. For a process to be cost effective, the key factors involves selection of shortest reaction pathway, use of inexpensive raw materials or reagents, avoiding polluting and corrosive reagents, avoid the formation of side products, improving reaction conversions by optimizing reaction dilutions and reagent mole ratios, good isolation procedures, improve atom efficiency which has greater chances of meeting tough demand both from cost and environmental perspective.

1.2.2: Role of Related substances or Impurities

Related substance or an impurity play an important role in drug development. Impurity is defined as unwanted material that is present apart from drug substance and excipients. These impurities are formed
during synthesis of drug substances, formulation of drug product or during storage. The safety and efficacy of a drug product depends upon the levels of impurities present in the drug substance or drug product. Different Pharmacopoeias and The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)\textsuperscript{38} are insisting to incorporate the limits for impurities in the specifications.

Based on the stringent regulatory requirements, it is mandatory to identify, control and quantify the levels of impurities during product development. It is more challenging for an organic chemist to identify impurities which are formed in low levels in drug substance. Since most of the time it is very difficult to control and identify the impurity within the acceptable levels in the process, extra purification steps may then be necessary thereby making the process less competitive. More often, the synthetic procedure for impurities are not reported in literature which makes it even more difficult for the organic chemist to design a synthesis which is time consuming. The development of drug substance is incomplete without identification of impurity profile involved in the process. Moreover, it is not mandatory to design novel synthetic routes for the impurities.

In summary, it is very essential to develop a process which is free from impurities to improve the safety and efficacy of the product and also to
identify, synthesize and qualify the possible impurities in drug substance or drug product.

1.3: Conclusions

Drug substances play a vital role in human life. Among the active drug substances, Montelukast, Sildenafil, Sertindole and Levocetirizine are having specific importance based on the commercial value. Hence, the proposed research work was extensively carried out in exploring alternate synthetic routes to these drug substances. Also, in our further endeavour, we have identified and synthesized the possible related substances formed during the synthesis.