PREFACE

With its grounding in the "guiding pillars of Access, Equity, Equality, Affordability and Accountability," the New Education Policy (NEP 2020) envisions flexible curricular structures and creative combinations for studies across disciplines. Accordingly, the UGC has revised the CBCS with a new Curriculum and Credit Framework for Undergraduate Programmes (CCFUP) to further empower the flexible choice based credit system with a multidisciplinary approach and multiple/ lateral entry-exit options. It is held that this entire exercise shall leverage the potential of higher education in three-fold ways – learner's personal enlightenment; her/his constructive public engagement; productive social contribution. Cumulatively therefore, all academic endeavours taken up under the NEP 2020 framework are aimed at synergising individual attainments towards the enhancement of our national goals.

In this epochal moment of a paradigmatic transformation in the higher education scenario, the role of an Open University is crucial, not just in terms of improving the Gross Enrolment Ratio (GER) but also in upholding the qualitative parameters. It is time to acknowledge that the implementation of the National Higher Education Qualifications Framework (NHEQF) National Credit Framework (NCrF) and its syncing with the National Skills Qualification Framework (NSQF) are best optimised in the arena of Open and Distance Learning that is truly seamless in its horizons. As one of the largest Open Universities in Eastern India that has been accredited with 'A' grade by NAAC in 2021, has ranked second among Open Universities in the NIRF in 2024, and attained the much required UGC 12B status, Netaji Subhas Open University is committed to both quantity and quality in its mission to spread higher education. It was therefore imperative upon us to embrace NEP 2020, bring in dynamic revisions to our Undergraduate syllabi, and formulate these Self Learning Materials anew. Our new offering is synchronised with the CCFUP in integrating domain specific knowledge with multidisciplinary fields, honing of skills that are relevant to each domain, enhancement of abilities, and of course deep-diving into Indian Knowledge Systems.

Self Learning Materials (SLM's) are the mainstay of Student Support Services (SSS) of an Open University. It is with a futuristic thought that we now offer our learners the choice of print or e-slm's. From our mandate of offering quality higher education in the mother tongue, and from the logistic viewpoint of balancing scholastic needs, we strive to bring out learning materials in Bengali and English. All our faculty members are constantly engaged in this academic exercise that combines subject specific academic research with educational pedagogy. We are privileged in that the expertise of academics across institutions on a national level also comes together to augment our own faculty strength in developing these learning materials. We look forward to proactive feedback from all stakeholders whose participatory zeal in the teaching-learning process based on these study materials will enable us to only get better. On the whole it has been a very challenging task, and I congratulate everyone in the preparation of these SLM's.

I wish the venture all success.

Professor Indrajit Lahiri
Vice-Chancellor

NETAJI SUBHAS OPEN UNIVERSITY

Four Year Undergraduate Degree Programme
Under National Higher Education Qualifications Framework (NHEQF) & Curriculum and Credit Framework for Undergraduate Programmes

Course Type: Skill Enhancement Courses (SEC)

Course Title: Pharmaceutical Chemistry

Course Code: NSE-CH-01

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CONTENT

Unit 1 : Drug Discovery, Design and Development

1.0 Objectives

To provide an overview of the key concepts and stages in drug discovery, design, and development, including target identification, lead optimization, preclinical and clinical trials, and regulatory approval, with a focus on modern strategies and challenges in pharmaceutical research.

1.1 Introduction

Pharmaceutical chemistry (medicinal chemistry) is the study of drugs, and its development. This also includes drug discovery, delivery, absorption, metabolism, and more. There are many of biomedical analysis, pharmacology, pharmacokinetics, and pharmacodynamics. Medicinal chemistry work is usually done in a laboratory framework. This chemistry involves cures and therapies for disease, analytical techniques, pharmacology, metabolism, quality assurance, and drug chemistry.

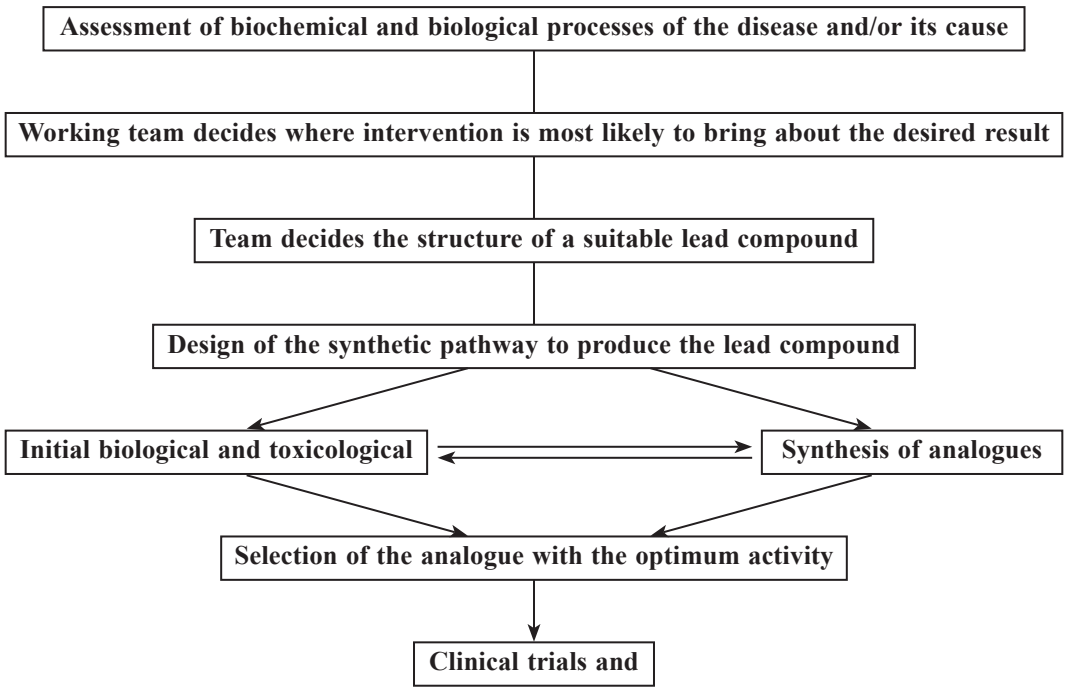
Now the question is what are drugs? And why do we need new ones? In this regards we can say Drugs are strictly defined as chemical substances that are used to prevent or cure diseases in humans, animals and plants. The activity of a drug is its pharmaceutical effect on the subject, for example, analgesic or β-blocker, whereas its potency is the measurable nature of that effect. Regrettably, the term drug is also used by the media and the general public to describe the substances taken for their psychotic rather than medicinal effects. However, this does not mean that these substances cannot be used as drugs. Heroin, for example, is a very effective painkiller and is used as such in the form of diamorphine in late-stage cancer cases.

1.2 Drug Discovery

In drug discovery process the new class of medications are discovered. The discovery of a new drug includes not only a discovery or design process but also the synthesis of drug, a method of administration, the improvement of tests and procedures to establish how it operates in the body and its safety assessment. Discovery of a new drug may also require fundamental research into the chemical and biological nature of the diseased state. Recent drug discovery involves the identification of target hit, medicinal chemistry and optimization of those hits to increase the affinity, selectivity i.e. to reduce the potential of side effects, oral bioavailability and metabolic stability i.e. to increase the half-life. The process of drug development can continue once a compound fulfills all of these requirements. Thus, Drug discovery is the process of finding new medicines. It can happen in different ways:

- By studying natural substances (plants, bacteria, marine organisms, etc.)
- By modifying existing drugs to improve their effects.
- By designing new molecules using computer simulations.
- By screening thousands of chemical compounds to find potential drugs.

A flowchart includes the general steps followed in the discovery of a new drug for a specific disease state is shown below.



1.3 Historical outline

Long ago the peoples of the world have had a wide range of natural products that they use for medicinal purposes. These products obtained from mineral sources, vegetable and from animals. However, these products were sometimes very effective but many of the products were toxic also. Information about these ancient remedies was not readily to users until the invention of the printing press in the fifteenth century. The early nineteenth century saw the extraction of pure substances from the plant materials. Though these substances were of consistent quality but only a few of the isolated compound proved to be satisfactory as therapeutic agents. Although, morphine and cocaine for example, were extensively prescribed by the physicians but the majority were found to be too toxic. In the late 19^{th} the search to find fewer toxic medicines than those based on natural sources resulted in the introduction of synthetic substances as drugs. More recently, discovery of a drug includes classical pharmacology (i.e. chemical libraries of synthetic small molecules, natural products were screened in intact cells or whole organism to identify substances that had a desirable therapeutic effect), after that reverse pharmacology and efficacy. Modern drug discovery is thus usually a capital-intensive process that involves large investments by pharmaceutical industry and governments corporations.

The scientists led to the conclusion that individual chemicals are required for the biological activity of the drug from the effect of a drug in the human body is mediated by specific interactions of the drug molecule with biological macromolecules. This made for the beginning of the modern era in pharmacology, as pure chemicals, instead of crude extracts of medicinal plants, became the standard drugs. Later, small molecules were synthesized to specifically target a known physiological pathway, avoiding the mass screening of banks of stored compounds. This led to great success, such as the work of Gertrude Elion and George H. Hitchings on purine metabolism. Now-a-days, reverse pharmacology is the most frequent approach used, is the cloning of human proteins made possible the screening of large libraries of compounds against specific targets thought to be linked to specific diseases.

1.4 Different Stages of Drug Discovery

Introducing a new drug to market is a complex and time-consuming procedure that can cost pharmaceutical companies an average $2.6 billion and ten years of research and development. There are multiple defined stages for this process, each with their own associated challenges, timelines, and costs. In general, to find out one effective drug molecule more than 10000 molecules need to take into consideration during this procedure. Before preclinical development target discovery and its validation followed by Lead Compound Identification and optimization are the primary criteria of drug discovery. In preclinical development i.e in stage-2 the molecules are examined on different states of animals. In stage 3 i.e clinical trial scientists need to consider many phases to find out right choice. During this time different parameter like effect on human bodies, safety, efficacy, effectiveness on diseases, large scale safety and effectiveness and of course long-term safety carefully checked. Finally, regulatory approval from FDA or CDC could lead the drugs in the market. During this time Post-Approval Research & Monitoring also been carried out because what most of the population does not realize is the amount of post-approval monitoring that pharmaceutical companies need to conduct while their drug is on the market. Some data obtained from this phase are unpredicted serious side effects, interactions with other drugs, potential alternate uses, and modifications to dosage.

1.5 Drug Design & Development

The design and development of a drug involves a systematic approach to identifying, optimizing, and producing a drug candidate that is both safe and effective.

This process follows from initial discovery to final production and marketing. It is broadly divided into two key stages—(i) Drug Designing (Early-Stage Development), (ii) Drug Development (Late-Stage Development)

1.5.1. Drug Designing

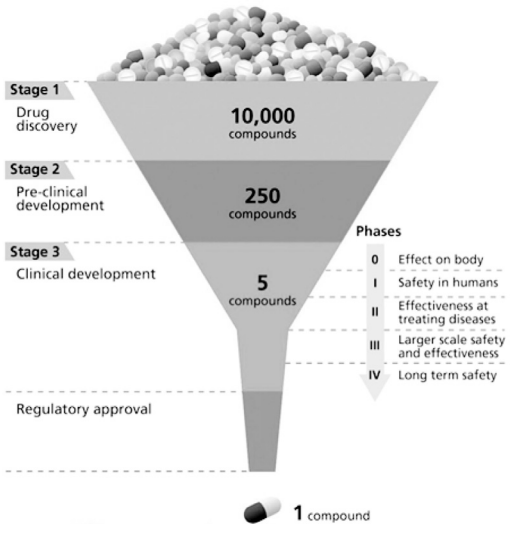
The approach of finding drugs by design, based on their biological targets is known as drug design, sometimes referred to as rational drug design. Typically, a drug target is a key molecule involved in a particular metabolic pathway that is specific to a disease condition. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as protein, which in turn results in a therapeutic benefit to the patient.

What is really meant by drug design is ligand design i.e. design of a small molecule that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. In medicine, biotechnology and pharmacology, drug discovery is the process by which drugs are designed.

➢ Methodologies in Drug Design

There are several key methodologies employed in drug design, each with its own unique approach:

i) **Ligand-Based Drug Design :** Relies on knowledge of other molecules that bind to the biological target of interest. It is used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.



ii) **Structure-Based Drug Design :** Relies on knowledge of three-dimensional (3D) structure of the biological target obtained through X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy.

iii) **Mechanism-Based Drug Design :** When the disease process is understood at the molecular level and the target molecule(s) are defined, drugs can be designed specifically to interact with the target molecule.

iv) **Computer-Assisted Drug Design (CADD) :** Drug design frequently but not necessarily relies on computer modeling techniques. CADD represents computational methods and resources that are used to facilitate the design and discovery of new therapeutic solutions. Drug design with the help of computers may be used at any of the following stage of drug discovery.

- Hit identification using virtual screening.
- Hit-to-lead optimization of affinity and selectivity.
- Optimization of other pharmaceutical properties while maintaining affinity.

➢ Key Factors in Drug Design

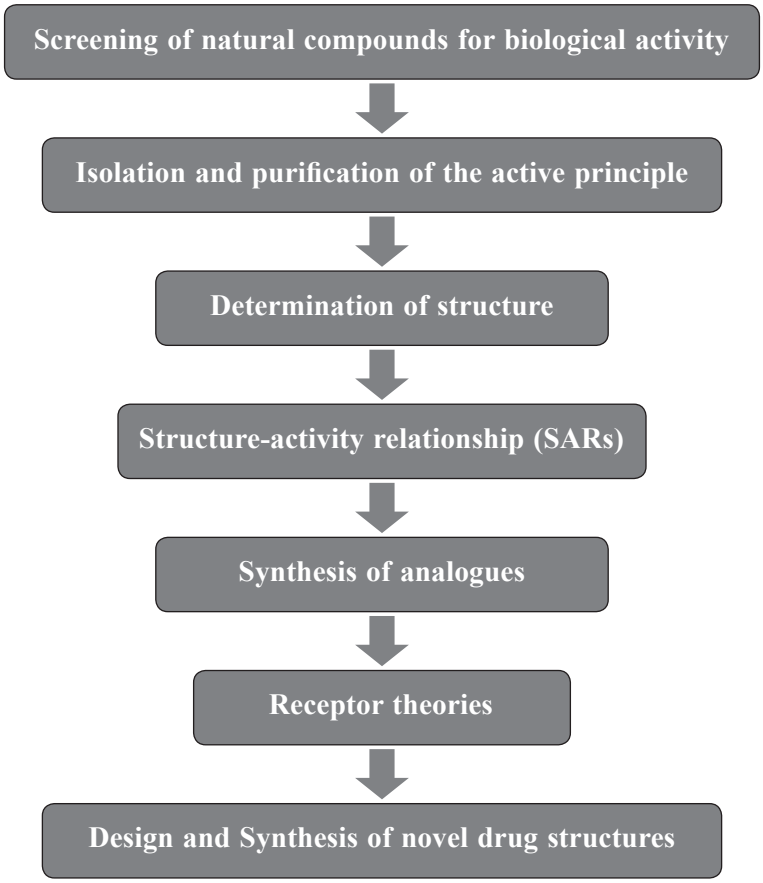
When designing a drug, several critical factors must be considered to ensure its effectiveness and safety:

- **Binding affinity :** How well the drug binds to its target.
- **Bioavailability :** How easily the drug dissolves and is distributed throughout the body.
- **Duration of action :** The length of time the drug remains active in the body.
- **Safety profile :** Possible side effects and the overall safety of the drug.

Together, these factors shape the development of a drug, helping to ensure its therapeutic success and minimize potential risks to patients.

1.5.2 Drug Development

It is the process of taking a new chemical lead (drug) through the stages necessary to allow it to be tested in human clinical trials, in its broadest definition this encompasses the entire process of finding a suitable molecular target and clinical testing of novel drug candidates. Since ancient time peoples have used herbs and potions as medicines and since then serious efforts were made to isolate and purify the active principles of these remedies and a large variety of biologically active compounds have been obtained and their structures determined (e.g. quinine from the bark of the cinchona tree, morphine of opium, cocaine from coca leaves). These natural products became the lead compounds for a major synthetic effort where chemists literally made thousands of analogues in an attempt to improve on with Nature had provided. Now-a-days, the development of a novel drug from natural sources might follow the following pattern.



1.6 Classification of Drugs

Drugs can be grouped together in different ways – by the way they affect the body or by how or where they are used. Though different text books grouped drugs in different ways thus their classifications are quite confusing. Normally drugs are classified in following four ways—

i) **Classification on the basis of pharmacological effect or therapeutic action :**

How a drug or medicine affects or influences the cells of an organism is referred to as the pharmacological effect. Drugs are grouped depending on the biological effect they have. Different types of drugs have various pharmacological effects on an organism. For example, an analgesic reduces pain while an anti-inflammatory drug reduces inflammation in the body.

ii) Classification on the basis of drug action :

Drugs are grouped according to the enzyme or receptor with which they interact. Different drugs act differently i.e. each drug has its own way of generating a response. For example, there are lots of medicines to treat hypertension but they have different drug action such as all medicines of hypertension reduces the blood pressure but in a different way.

iii) Classification on the basis of chemical structure :

Drugs which have a common skeleton are grouped together. Generally, drugs that have the same pharmacological effect and drug action have a basic skeleton structure and a minute variation in the branching. For example, all sulphonamides have the same skeleton structure.

iv) Classification on the basis of molecular targets :

These are compounds which are grouped according to whether they affect a certain target system in the body. Usually, drugs target the macromolecules inside the body to generate a biological response. Drugs that have the same mechanism of action will have the same target.

1.7 Basic Retro-synthetic Approach

In pharmaceutical chemistry, the retro-synthetic approach is a method used to design the synthesis of complex drug molecules by breaking them down into simpler structures. This technique helps chemists plan the best way to create a drug from readily available starting materials. It plays a vital role in drug discovery by allowing scientists to develop new medicines efficiently.

1.7.1 Steps in Retro-synthetic Analysis for Drug Discovery

1. **Identify the Target Drug Molecule:** The final compound that needs to be synthesized.
2. **Break Down the Molecule:** Reduce the complexity by identifying key bonds that can be disconnected.
3. **Find Suitable Precursors:** Identify simpler molecules that can be used to construct the target drug.
4. **Repeat the Process:** Keep breaking down until commercially available or easily synthesizable molecules are obtained.
5. **Forward Synthesis:** Once the breakdown is complete, use the identified steps to synthesize the drug step-by-step.

1.7.2. Example of Retro-synthesis in Drug Discovery

Now we take the example of Retro-synthesis of the Drug Paracetamol i.e. a Pain Reliever & Fever Reducer

- **Target Molecule :** Paracetamol (Acetaminophen)
- **Disconnection :** Paracetamol can be broken into 4-aminophenol and acetic anhydride.
- **Precursors :** 4-Aminophenol can be derived from nitrobenzene, and acetic anhydride is a common reagent.
- **Synthesis :** 4-Aminophenol reacts with acetic anhydride to form Paracetamol.

1.7.3. Importance of Retro-synthetic Approach in Drug Discovery

Importance of Retro-synthetic Approach in Drug Discovery is as follows

- Helps in designing efficient synthetic routes for drug manufacturing.
- Reduces waste and increases yield in pharmaceutical production.
- Aids in modifying existing drugs to create better versions.
- Saves time and cost by using readily available starting materials.
- Useful for developing alternative synthesis methods when raw materials are scarce.

1.8 Summary

- Drug discovery involves the identification and development of new medications through various approaches, including studying natural substances, modifying existing drugs, and using computer-aided design. The process includes target identification, lead optimization, and safety assessment before advancing to preclinical and clinical trials.
- Historically, medicines were derived from natural sources, but advances in chemistry led to synthetic drug development. Modern drug discovery relies on high-throughput screening, computational modeling, and reverse pharmacology to design targeted therapies efficiently.
- Drug development follows a multi-stage process, including preclinical research, clinical trials, and regulatory approval. This lengthy and expensive process ensures the safety, efficacy, and quality of new drugs before they reach the market. Post-approval monitoring continues to assess long-term effects and potential improvements.

- Drug design involves rational approaches such as ligand-based, structure-based, mechanism-based, and computer-assisted methods to optimize drug-target interactions. Key factors include binding affinity, bioavailability, safety, and therapeutic effectiveness.
- Drugs are classified based on their therapeutic action, chemical structure, mode of action, and molecular targets. The retro-synthetic approach aids in drug synthesis by breaking complex molecules into simpler components, facilitating efficient manufacturing and development of improved medicines.

1.9 Exercises

A. Short Answer Questions

1. What is drug design?
2. What are the key factors considered in drug design?
3. What are the different phases of clinical trials in drug development?
4. What is the retro-synthetic approach in drug discovery?
5. Why is retro-synthesis important in pharmaceutical chemistry?
6. Explain the basic steps of retro-synthesis.
7. Provide a simple retro-synthetic analysis of Paracetamol.
8. What are the advantages and limitations of CADD compared to traditional drug discovery methods?
9. Give an example of how a pharmacophore model is used in Ligand-Based Drug Design.
10. Explain the significance of Mechanism-Based Drug Design in drug discovery.

B. Multiple Choice Questions (MCQs)

1. Which of the following is NOT a factor considered in drug design?

   a) How well the drug binds to the target b) The price of the drug c) How long the drug remains active d) Possible side effects

Answers: b

2. What is the main goal of retro-synthetic analysis?

   a) To create complex molecules from simpler ones b) To break down drug molecules into smaller parts for synthesis c) To increase the cost of drug production d) To eliminate the need for synthesis

Answers: b

3. Which of the following is an example of a precursor in Paracetamol synthesis?

   a) Acetic acid b) 4-Aminophenol c) Benzene d) Ethanol

Answers: b

4. Which step comes first in retro-synthesis?

   a) Forward synthesis b) Identifying the target drug molecule c) Testing on animals d) Selling the drug

Answers: b

5. Which of the following is an example of a natural product-derived drug?

   a) Paracetamol, b) Ibuprofen, c) Quinine, d) Aspirin

Answer: c

6. Which methodology in drug design relies on knowledge of other molecules that bind to the biological target?

   a) Structure-Based Drug Design, b) Ligand-Based Drug Design, c) Mechanism-Based Drug Design, d) Computer-Assisted Drug Design

Answer: b

Unit 2 : Antacids - A Remedy for Acidity

2.0 Objectives

By the end of this unit, students will be able to—

- Understand the Concept of Acidity and explain the causes, symptoms, and effects of acidity in the human digestive system.
- Define Antacids , describe what antacids are and their role in neutralizing stomach acid.
- Identify Common Antacid Compounds, list commonly used antacid ingredients such as magnesium hydroxide, aluminum hydroxide, calcium carbonate, and sodium bicarbonate.
- Explain the Mechanism of Action, illustrate how antacids work to relieve acid reflux and indigestion.
- Evaluate the Uses and Side Effects, discuss the benefits, potential side effects, and precautions associated with prolonged antacid use.

2.1 Introduction

Acidity is a common condition affecting millions of people worldwide. It occurs when the stomach produces excessive gastric acid, leading to discomfort, heartburn,

and indigestion. One of the most effective ways to counteract acidity is through the use of antacids. These medications help neutralize stomach acid, providing quick relief from acid-related discomfort. Here we will learn about antacids.

2.2 Antacids

Antacids are a type of medication used to neutralize stomach acid and relieve symptoms associated with acid reflux, heartburn, and indigestion. These conditions occur when excess acid in the stomach irritates the lining of the esophagus or the stomach itself. Antacids work by increasing the pH level in the stomach, making it less acidic, which helps to soothe the irritation and discomfort.

Most antacids contain basic (alkaline) substances, such as sodium bicarbonate, calcium carbonate, magnesium hydroxide, or aluminum hydroxide. These ingredients react with the hydrochloric acid in the stomach, forming water and other neutral compounds, thereby reducing the acidity.

2.3 History of Antacids

The use of substances to alleviate acidity-related ailments dates back to ancient times. In historical texts, various civilizations, including the Greeks and Egyptians, used alkaline substances like chalk and crushed coral to counteract stomach acidity. Modern antacids evolved in the 19^{th} and 20^{th} centuries with the development of compounds such as magnesium hydroxide and aluminum hydroxide. The pharmaceutical industry has since refined these formulations for increased efficacy and reduced side effects.

2.4 Chemistry of Antacids

Antacids primarily contain weak bases that neutralize hydrochloric acid (HCl) in the stomach. The most common active ingredients include:

1. **Sodium Bicarbonate ($NaHCO_3$) :** Reacts with stomach acid to produce carbon dioxide and water, providing rapid relief but may cause bloating.
2. **Calcium Carbonate ($CaCO_3$) :** A strong and long-lasting neutralizer, though excessive use can lead to kidney stones.
3. **Magnesium Hydroxide ($Mg(OH)_2$) :** Commonly known as milk of magnesia, provides fast relief but may have a laxative effect.
4. **Aluminum Hydroxide ($Al(OH)_3$) :** Works slower than magnesium-based antacids but is gentler on the digestive system.

5. **Combination Formulations :** Many commercial antacids contain a mix of these compounds to balance their effects and minimize side effects.

Antacids neutralize stomach acid through simple acid-base reactions—

- **Sodium Bicarbonate :** $NaHCO_3 + HCl \rightarrow NaCl + CO_2 + H_2O$
- **Calcium Carbonate :** $CaCO_3 + 2HCl \rightarrow CaCl_2 + CO_2 + H_2O$
- **Magnesium Hydroxide :** $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$
- **Aluminum Hydroxide :** $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$

2.5 Magnesium silicate (an Antacid)

Antacids are generally weak bases or basic salts which neutralizes stomach acidity. They are used to relieve acid indigestion, upset stomach, sour stomach and heart-burn. Most antacids are weak inorganic bases. More specifically, magnesium silicate acts as a neutralizing and astringent agent. It is the magnesium salt of silicic acid containing an unspecified amount of water. The molecular formula can be expressed more clearly as $MgSiO_3.XH_2O$. It is known as'Talc'and its presents many uses in the cosmetic industry, food industry and pharmaceutical industry.

Magnesium silicate is prepared by the precipitation reaction between sodium silicate (Na_2SiO_3) dissolved in water and a magnesium salt [$Mg(NO_3)_2.6H_2O$] was dissolved in the mixture of propylene glycol-400 and ethanol. After those two solutions were mixed, a white precipitate was formed. The aqueous suspension of the precipitate is filtered and the product was collected.

2.6 Mechanism of Action of Antacids

Antacids function by increasing the pH level of gastric contents, reducing acidity and relieving symptoms like heartburn, indigestion, and acid reflux. Unlike proton pump inhibitors (PPIs) and H_2-receptor blockers, which reduce acid production, antacids work by directly neutralizing existing acid.

Some formulations also contain **alginate,** which forms a barrier over the stomach contents to prevent acid reflux. Others include **simethicone,** which helps reduce gas and bloating.

2.7 Types of Antacids

➢ **Systemic Antacids :** These antacids, such as sodium bicarbonate, Calcium Carbonate get absorbed into the bloodstream and can alter the body's pH balance.

➢ **Non-Systemic Antacids :** These include aluminum hydroxide and magnesium hydroxide, which remain in the digestive tract and do not affect overall pH balance.

2.8 Medical Uses of Antacids

1. **Gastroesophageal Reflux Disease (GERD) :** Antacids provide temporary relief from GERD symptoms but are not a long-term solution.
2. **Peptic Ulcer Disease :** Though not a primary treatment, antacids can help alleviate ulcer-related pain.
3. **Dyspepsia (Indigestion) :** Used to relieve bloating, nausea, and stomach discomfort.
4. **Calcium Supplementation :** Calcium carbonate-based antacids serve as a supplementary calcium source, particularly for individuals at risk of osteoporosis.
5. **Kidney Disease Management :** Aluminum hydroxide is sometimes used to bind excess phosphate in kidney disease patients.

2.9 Side Effects and Risks

While generally safe for short-term use, antacids can cause side effects, especially when overused:

- **Metabolic Alkalosis :** Excessive intake of bicarbonate-based antacids can disrupt the body's pH balance.
- **Electrolyte Imbalance :** Long-term use of magnesium-based antacids may lead to hypermagnesemia, while aluminum-based ones can cause hypophosphatemia.
- **Kidney Stones :** High doses of calcium carbonate can contribute to kidney stone formation.
- **Diarrhea or Constipation :** Magnesium-based antacids may cause diarrhea, whereas aluminum-based ones often lead to constipation.
- **Rebound Acid Hypersecretion :** A sudden stop in antacid use may result in excessive acid production.

2.10 Precautions While Using Antacids

- Do not exceed the recommended dosage.

- Consult a doctor if symptoms persist for more than two weeks.
- Avoid long-term use without medical supervision.
- Be cautious if you have kidney disease, as some antacids contain high levels of minerals.
- Check for interactions with other medications, as antacids can interfere with the absorption of certain drugs.

2.11 Summary

Antacids serve as a quick and effective remedy for acid-related issues. While they provide relief from heartburn, indigestion, and acid reflux, it is important to use them responsibly. Lifestyle changes, such as maintaining a healthy diet, reducing stress, and avoiding spicy foods, can also help in managing acidity. Always seek medical advice for persistent symptoms to ensure proper treatment.

2.12 Exercises

Multiple Choice Questions (MCQs)

1. What is the primary function of antacids?
   a) Increase stomach acid production
   b) Neutralize stomach acid
   c) Promote acid secretion
   d) Inhibit bacterial growth

Answer : b) Neutralize stomach acid

2. Which of the following antacids is most likely to cause constipation?
   a) Magnesium hydroxide
   b) Calcium carbonate
   c) Aluminum hydroxide
   d) Sodium bicarbonate

Answer : c) Aluminum hydroxide

3. What gas is produced when sodium bicarbonate reacts with hydrochloric acid?
   a) Oxygen
   b) Nitrogen
   c) Carbon dioxide

d) Hydrogen

Answer : c) Carbon dioxide

Short Answer Questions

4. Explain the mechanism of action of antacids.
5. Differentiate between aluminum-based and magnesium-based antacids.
6. List three common side effects of antacid overuse.

Long Answer Questions

7. Describe the chemical reactions involved in antacid action with suitable examples.
8. Discuss the advantages and disadvantages of different types of antacids.
9. Explain the role of antacids in managing acid-related disorders and their limitations.

Unit 3: Synthesis of the representative drugs

3.0 Objectives

By the end of this unit, students will be able to:

- Understand Drug Classes, define and differentiate between analgesic, antipyretic, and anti-inflammatory agents.

- Explain Synthetic Routes, describe the step-by-step chemical synthesis of aspirin, paracetamol, and ibuprofen.
- Analyze Reaction Mechanisms, understand the key chemical reactions, reagents, catalysts, and conditions involved in the synthesis of these drugs.

3.1 Introduction

The synthesis of pharmaceutical compounds is a crucial aspect of medicinal chemistry. Analgesic, antipyretic, and anti-inflammatory agents are commonly used drugs for pain relief, fever reduction, and inflammation management. This chapter discusses the synthesis of three representative drugs: Aspirin (Acetylsalicylic Acid), Paracetamol (Acetaminophen), and Ibuprofen.

3.2 Analgesics Agents

Analgesics, commonly known as painkillers, are medications used to relieve pain without causing loss of consciousness. They work by either blocking pain signals to the brain or reducing the production of pain-inducing chemicals. Analgesics are broadly classified into **opioid analgesics** and **non-opioid analgesics,** based on their mechanism of action and potency. This classification distinguishes analgesics from anesthetics.

- **Analgesics :** Drugs that selectively relieve pain by acting on the central nervous system (CNS) or peripheral pain mechanisms without significantly altering consciousness.
- **Anesthesia :** A state of loss of sensation. Anesthetic agents induce the loss of all sensory modalities, particularly pain, often accompanied by reversible loss of consciousness.
- **Pain (Algesia) :** An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

3.2.1 Classification of Analgesics

Analgesic can be classified mainly two categories based on their mechanism of action—

A. Opioid (Narcotic) Analgesics

Opioid analgesics, also known as narcotic analgesics, are powerful pain-relieving drugs that act on the central nervous system (CNS) by binding to opioid

receptors in the brain and spinal cord. They are used for moderate to severe pain but have a high potential for tolerance, dependence, and addiction. Examples include—

- Morphine
- Codeine
- Fentanyl

B. Non-Opioid (Non-Narcotic) Analgesics/NSAIDs

Non-opioid analgesics, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), are medications that relieve pain without affecting the central nervous system like opioids. They primarily work by reducing inflammation and inhibiting prostaglandin synthesis, making them effective for mild to moderate pain, fever, and inflammation. Examples include—

- Aspirin
- Paracetamol
- Ibuprofen

Comparison between Opioid vs. Non-Opioid Analgesics can be given in the following table.

Feature	Non-Opioid Analgesics	Opioid Analgesics
Mechanism	Inhibit prostaglandins	Act on opioid receptors
Pain Type	Mild to moderate pain	Moderate to severe pain
Addiction Risk	Low	High
Examples	Paracetamol, NSAIDs	Morphine, Tramadol

Analgesics function by either reducing inflammation or directly affecting pain perception. Anti-inflammatory drugs relieve pain by minimizing local inflammatory responses, while opioids act on the brain to modify pain perception.

Opioid analgesics, historically referred to as narcotics, can induce sleep and are used for both short-term and long-term relief of severe pain. In contrast, anti-inflammatory drugs (NSAIDs) are primarily used for short-term pain relief in cases of mild to moderate pain, such as headaches, muscle strain, bruising, or arthritis.

3.2.2 Mechanism of Action of Analgesics

Analgesics work by blocking pain signals or reducing inflammation, depending on their type. They can act on the central nervous system (CNS) or the peripheral nervous system (PNS) to relieve pain.

3.2.3 Clinical Uses of Analgesics

- Relief from mild to severe pain (e.g., headache, arthritis, surgery)
- Fever reduction (paracetamol, aspirin)
- Inflammation management (NSAIDs like ibuprofen)

3.2.4 Side Effects of Analgesics

- Opioids: Respiratory depression, addiction, nausea
- NSAIDs: Gastrointestinal ulcers, kidney damage
- Paracetamol: Liver toxicity in high doses

3.3. Anti-inflammatory agent

Most anti-inflammatory analgesics originate from three compounds discovered in the 19th century: Salicylic Acid, Pyrazolone, and Phenacetin (Acetophenetidin). Though chemically distinct, these compounds relieve mild to moderate pain by reducing inflammation at its source. Among them, Acetylsalicylic Acid (Aspirin), derived from salicylic acid, is the most widely used and serves as the prototype for anti-inflammatory analgesics. Other major types include acetaminophen (a phenacetin derivative) and nonsteroidal anti-inflammatory drugs (NSAIDs), such as Ibuprofen, Naproxen, and Fenoprofen. Pyrazolone derivatives, with few exceptions, have been largely discontinued due to their association with agranulocytosis, a severe infection.

Aspirin and NSAIDs share a common molecular mechanism—inhibiting prostaglandin synthesis, which plays a key role in inflammation. This occurs through the suppression of cyclooxygenase (COX) enzymes

- **COX-1** is present in most normal tissues.
- **COX-2** is induced during inflammation.

Since COX-2 is not typically found in the stomach, COX-2 inhibitors (e.g., Rofecoxib, Celecoxib) cause less gastric ulceration than aspirin and other NSAIDs. However, unlike nonselective COX inhibitors, COX-2 inhibitors do not prevent blood clot formation, a key benefit of aspirin. Many aspirin-like analgesics, including Indomethacin and Sulindac (derived from the heterocyclic compound indole), also inhibit prostaglandin synthesis.

Inflammation is the body's natural response to injury, infection, or harmful stimuli, aiding in pathogen elimination, tissue repair, and homeostasis. However, chronic inflammation can contribute to diseases like arthritis, asthma, and cardiovas-

cular disorders. Anti-inflammatory agents help mitigate inflammation by targeting specific biochemical pathways, reducing pain and preventing complications.

3.4 Classification of Anti-Inflammatory Agents

Anti-inflammatory agents can be broadly classified into two major categories:

i. Steroidal Anti-Inflammatory Drugs (SAIDs)
ii. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

3.4.1 Steroidal Anti-Inflammatory Drugs (SAIDs)

Steroidal anti-inflammatory drugs, commonly known as corticosteroids, mimic the action of cortisol, a hormone produced by the adrenal cortex. These drugs exert potent anti-inflammatory effects by inhibiting phospholipase A2, thereby reducing prostaglandin and leukotriene synthesis. Examples are—

- Prednisolone
- Dexamethasone
- Hydrocortisone
- Methylprednisolone

SAIDs work by blocking inflammation at the genetic level. Their primary mechanism involves inhibiting phospholipase A_2, an enzyme responsible for producing inflammatory chemicals called prostaglandins and leukotrienes.

3.4.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are widely used for pain relief, fever reduction, and inflammation control. They work by inhibiting cyclooxygenase (COX) enzymes, reducing the production of prostaglandins, which are mediators of inflammation. E.g.

- Aspirin (Acetylsalicylic Acid)
- Ibuprofen
- Naproxen
- Diclofenac
- Celecoxib (Selective COX-2 inhibitor)

NSAIDs work by blocking two enzymes—

i) COX-1: Reduces protective prostaglandins, which can lead to stomach irritation and affect kidney function.
ii) COX-2: Lowers inflammatory prostaglandins, helping to reduce pain, swelling, and fever.

3.5 Natural Anti-Inflammatory Agents

Apart from synthetic drugs, several natural compounds exhibit anti-inflammatory properties—

- **Curcumin (Turmeric) :** Inhibits NF-κB and COX enzymes
- **Gingerol (Ginger) :** Reduces prostaglandin synthesis
- **Omega-3 Fatty Acids (Fish oil) :** Inhibits inflammatory cytokines
- **Resveratrol (Red wine, grapes) :** Modulates inflammatory pathways

3.6 Antipyretic Agents

Antipyretic agents are medications used to reduce fever (pyrexia) by lowering the body temperature. Fever is a natural defense mechanism of the body, often caused by infections, inflammatory conditions, or other medical disorders. While fever itself is not a disease, it can cause discomfort and, in extreme cases, lead to complications such as seizures, dehydration, and organ damage.

Antipyretic drugs act on the hypothalamus to regulate body temperature and are commonly used to provide symptomatic relief. They are widely used in conditions like influenza, bacterial infections, and post-vaccination fever.

3.6.1 Mechanism of Action of Antipyretic Agents

Antipyretics primarily work by inhibiting the production of prostaglandins, particularly prostaglandin E_2 (PEG_2), which plays a crucial role in raising the body's temperature set point in response to infection or inflammation. The key mechanisms include:

1. **Inhibition of Cyclooxygenase (COX) Enzymes :** Most antipyretics inhibit cyclooxygenase (COX-1 and COX-2) enzymes, which are responsible for prostaglandin synthesis.
2. **Reduction of PEG_2 Levels :** By inhibiting COX enzymes, antipyretics lower the levels of PEG_2 in the hypothalamus, thereby reducing the fever set point.
3. **Vasodilation and Heat Loss :** Many antipyretics induce vasodilation and sweating, which help dissipate heat and lower body temperature.

3.6.2 Classification of Antipyretic Agents

Antipyretics can be classified into different groups based on their chemical structure and mechanism of action—

1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the most common antipyretic agents. They work by inhibiting the COX enzymes and reducing prostaglandin synthesis. Some widely used NSAIDs include—

- **Paracetamol (Acetaminophen) :** Most commonly used antipyretic with mild analgesic properties.
- **Ibuprofen :** A widely used NSAID with strong anti-inflammatory and antipyretic effects.
- **Aspirin (Acetylsalicylic Acid) :** Effective but not recommended for children due to the risk of Reye's syndrome.
- **Naproxen :** Used for long-term pain and fever management.
- **Diclofenac :** Often used for post-surgical or inflammatory fever.

2. Selective COX-2 Inhibitors

Selective COX-2 inhibitors, such as celecoxib, are primarily used for their anti-inflammatory effects but can also have mild antipyretic properties.

3. Herbal and Natural Antipyretics

Several herbal remedies have antipyretic properties and are used traditionally for fever management:

- **Willow Bark (Salix alba) :** Contains salicylates, which have similar properties to aspirin.
- **Turmeric (Curcumin) :** Has anti-inflammatory and antipyretic effects.
- **Ginger :** Known for its fever-reducing properties.
- **Holy Basil (Tulsi) :** Used in Ayurveda for fever treatment.

3.6.3 Clinical Uses of Antipyretic Agents

Antipyretic drugs are used to manage fever associated with various conditions, including—

- Viral and bacterial infections **(e.g., flu, COVID-19, pneumonia)**
- Post-vaccination fever
- Inflammatory diseases **(e.g., arthritis, autoimmune disorders)**
- Febrile seizures in children
- Malaria and other parasitic infections

Commonly Used Antipyretic Drugs

Drug	Mechanism of Action	Common Uses	Side Effects
Paracetamol	Inhibits COX enzymes in the CNS	Fever, mild pain relief	Liver toxicity (overdose)
Ibuprofen	Inhibits COX-1 and COX-2	Fever, inflammation, pain	Gastric irritation, ulcers
Aspirin	Irreversibly inhibits COX-1 & COX-2	Fever, cardiovascular protection	Reye's syndrome (children)
Naproxen	Inhibits COX enzymes	Chronic pain, fever	Kidney damage (long-term use)

3.6.4 Side Effects of Antipyretic Drugs

While antipyretic agents are generally safe when used appropriately, they can have side effects, particularly with prolonged or excessive use—

- **Gastrointestinal Issues :** NSAIDs can cause stomach irritation, ulcers, and bleeding.
- **Liver Toxicity :** Paracetamol overdose can cause severe liver damage and even failure.
- **Kidney Damage :** Chronic use of NSAIDs can impair kidney function.
- **Reye's Syndrome :** Aspirin should not be used in children under 16 with viral infections due to the risk of this rare but serious condition.

3.6.5 Precautions for Antipyretic Drugs:

- Always take antipyretics with food to minimize gastric irritation.
- Follow recommended dosages to prevent toxicity.
- Avoid combining multiple NSAIDs to reduce the risk of side effects.
- Individuals with liver or kidney disorders should consult a doctor before use.

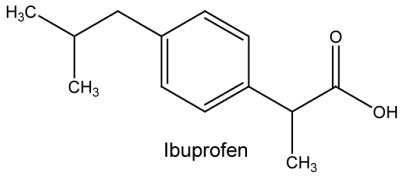
3.7. Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug used to relieve pain and reduce swelling, among other common treatments. It is somewhat short-lived and relatively mild. However, it is known to have an anti-platelet effect. In addition, ibuprofen acts as a vasoconstrictor because it inhibits the vasodilating prostacyclin that is produced by cyclooxygenase-2-enzymes. Ibuprofen is not only existing in tablet or capsule forms, but they can also be in topical gel form that can simply absorb through the skin, which are commonly use during sport injuries because it does not cause a high risk of digestive problems.

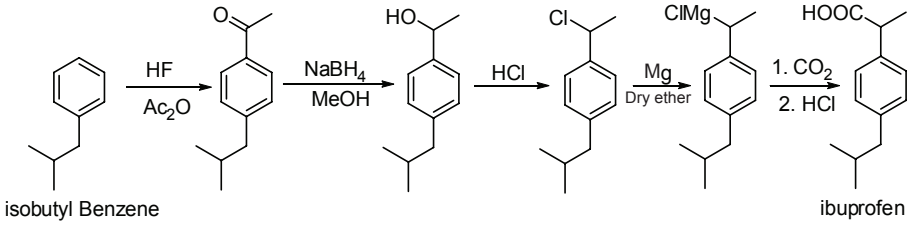
➢ Mechanism of Action

Ibuprofen inhibits both COX-1 and COX-2 enzymes, reducing prostaglandin synthesis. This results in decreased pain, fever, and inflammation.

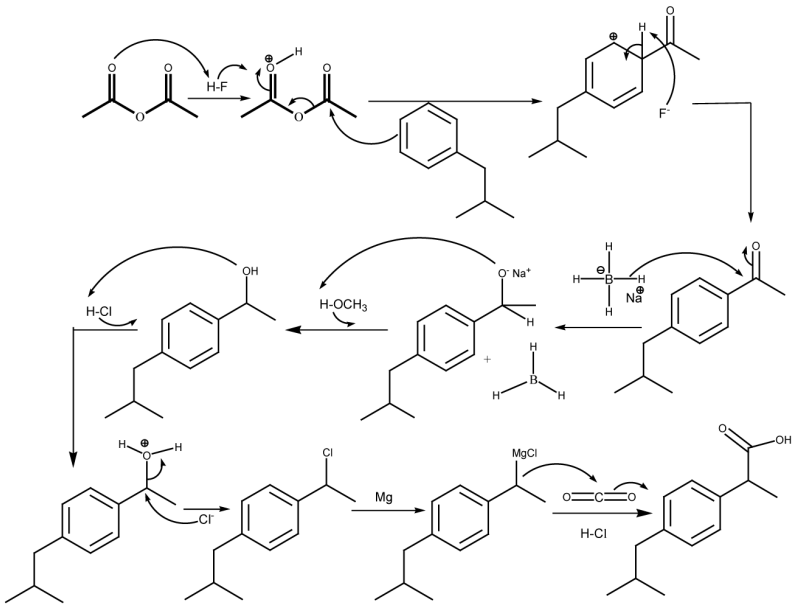
■ **Structure of Ibuprofen :**



■ **Synthesis of Ibuprofen :** The synthesis of ibuprofen was accomplished from isobutylbenzene. The synthetic process included a Friedel-Crafts acylation of isobutylbenzene afforded para-isobutyl Acetophenone, which under reduction condition followed by chloride substation form chlorinated product. After preparation of Grignard reagent, the precursor was trapped with CO_2 and after hydrolysis Ibuprofen was prepared.



■ **Reaction mechanism :**



➢ Clinical Uses of Ibuprofen

- Pain relief (e.g., headaches, muscle pain, menstrual cramps)
- Fever reduction
- Treatment of inflammatory conditions such as osteoarthritis and rheumatoid arthritis
- Postoperative pain management

➢ Side Effects of Ibuprofen

- Gastrointestinal irritation, ulcers, and bleeding
- Kidney damage with prolonged use
- Increased risk of cardiovascular events
- Allergic reactions such as rashes or anaphylaxis

3.8 Paracetamol (Acetaminophenol)

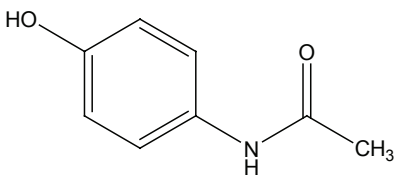
It is an effective antipyretic and analgesic. It is also active against arthritic and rheumatic disorders involving musculoskeletal pain as well as the pain occurred due to headache, myalgia, dysmenorrhea and neuralgia. Paracetamol also known as Acetaminophenol. In combination with Opioid pain medication, Paracetamol is now used for more severe pain such as cancer pain and after surgery, typically used either by mouth or rectally but is also available intravenously. Paracetamol is generally safe at recommended doses.

➢ Mechanism of Action of Paracetamol

Paracetamol primarily acts on the central nervous system (CNS) and exerts its effects through the following mechanisms:

1. **Inhibition of Cyclooxygenase (COX) :** Weakly inhibits COX-1 and COX-2 in peripheral tissues but significantly inhibits COX-3 in the brain, reducing prostaglandin E_2 (PEG_2) and lowering fever (antipyretic effect).
2. **Modulation of Pain Pathways :** Lowers prostaglandin levels in the CNS, increasing pain threshold (analgesic effect) and may also interact with the endocannabinoid system for additional pain relief..

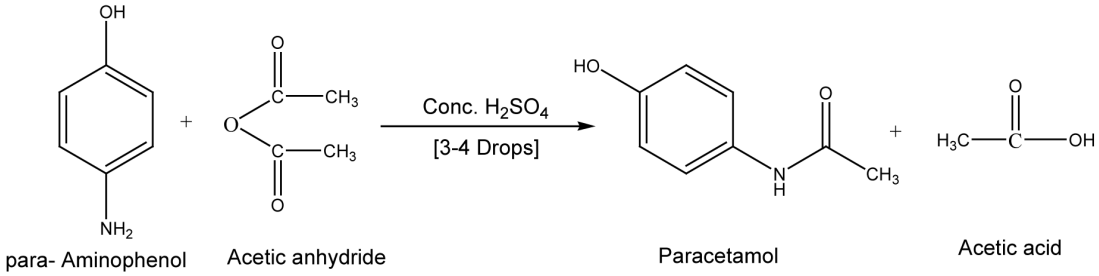
Structure of Paracetamol :



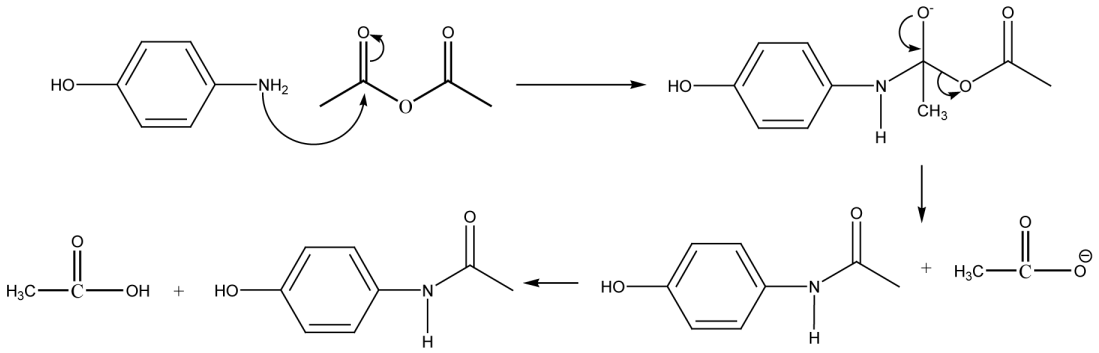
Paracetamol

Synthesis of Paracetamol :

Paracetamol is prepared from p-aminophenol by acetylating it with acetic anhydride in the presence of 3-4 drops of concentrated sulfuric acid as catalyst.



Reaction mechanism :



➢ Clinical Uses of Paracetamol

Paracetamol is used for :

1. **Fever Reduction :** Effective in treating fevers caused by infections, post-vaccination reactions, and inflammatory conditions.
2. **Pain Relief :** Used for mild to moderate pain, including: Headaches and migraines, various pain and cramps
3. **Combination Therapy :** Often combined with opioids (e.g., codeine) for enhanced pain relief.

Side Effects of Paracetamol :

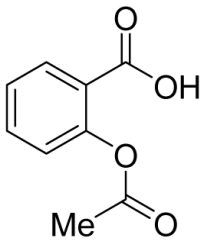
When used appropriately, paracetamol is generally well-tolerated. However, excessive use can lead to—

1. **Hepatotoxicity (Liver Damage) :** Risk factors include alcohol consumption, chronic use can cause liver disease.
2. **Renal Toxicity :** Long-term excessive use may impair kidney function.
3. **Allergic Reactions :** Rare cases of skin rashes, anaphylaxis, and Stevens-Johnson Syndrome (SJS).

3.9 Aspirin (Acetylsalicylic acid)

Aspirin is an effective analgesic (pain reliever), antipyretic (fever reducer) and anti-inflammatory agent and is one of the most widely used non-prescription drugs. The use of aspirin had its origin in the 18^{th} century, when it was found that an extract from the bark of willow trees was useful in reducing pain and fever. The active ingredient in willow bark was later found to be salicylic acid, was effective at reducing pain and fever, it also had some unpleasant side effects- it is irritating to the lining of the mouth, esophagus, stomach and can cause hemorrhaging of the stomach lining. Aspirin is also used long-term to help prevent further heart attacks, ischemic strokes and blood clots in people at high risk.

➢ Structure of Aspirin



Aspirin

➢ Mechanism of Action of Aspirin

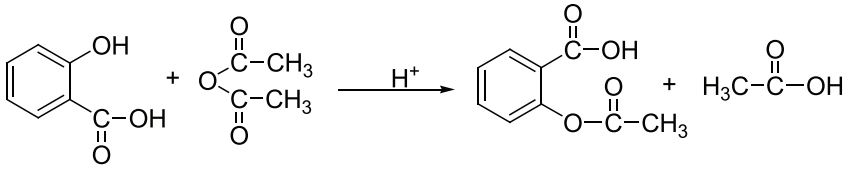
Aspirin exerts its effects through the inhibition of cyclooxygenase (COX) enzymes, leading to decreased production of prostaglandins and thromboxanes:

- **Analgesic and Antipyretic Action :** Aspirin inhibits COX-1 and COX-2, reducing prostaglandin E_2 (PEG_2) synthesis in the CNS. This leads to a reduction in pain and fever.
- **Anti-Inflammatory Action :** Inhibits prostaglandin synthesis at the site of inflammation. Reduces swelling, redness, and pain associated with inflammatory conditions.
- **Antiplatelet Effect :** Aspirin irreversibly inhibits COX-1 in platelets, leading to decreased production of thromboxane A_2 (TXA_2), preventing platelet aggregation. This property makes aspirin a crucial drug in the prevention of heart attacks and strokes.

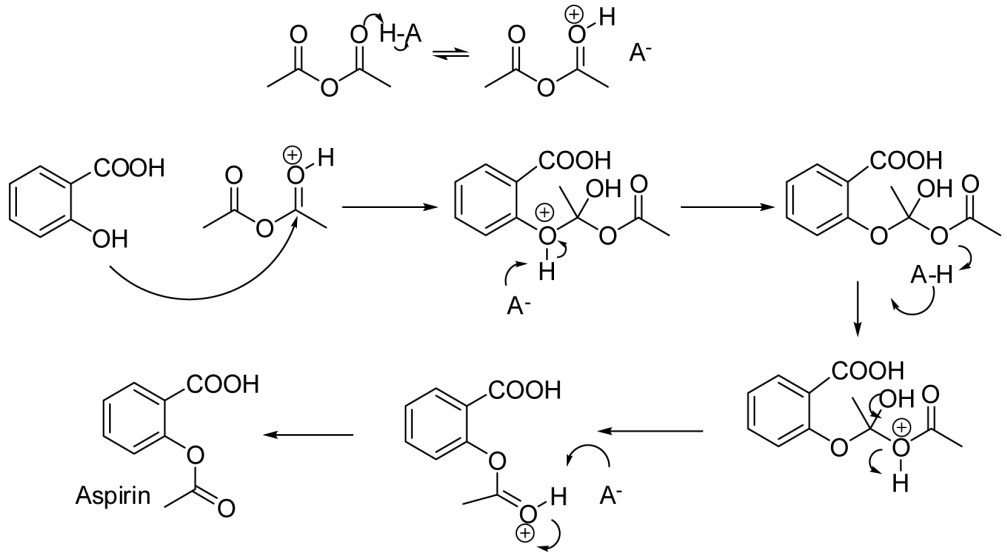
➢ Synthesis of Aspirin

The synthesis of aspirin is classified as an “Esterification Reaction”. Salicylic acid is treated with acetic anhydride, an acid derivative, undergoes a chemical

reaction that turns hydroxyl group of salicylic acid into an ester group (R-OH → R-OCOCH$_3$), yields aspirin and acetic acid (byproduct of this reaction) and a small amount of sulfuric acid (and occasionally phosphoric acid) are almost frequently used as a catalyst.



➢ Reaction mechanism



➢ Use of Aspirin

Aspirin is used for various medical conditions, including—

i) **Pain Relief :** Effective for mild to moderate pain, including: Headaches, Muscle pain, Dental pain, Arthritis pain

ii) **Fever Reduction :** Commonly used to lower fever in infections and inflammatory conditions.

iii) **Cardiovascular Disease Prevention :** Low-dose aspirin (75-100 mg) is used to prevent heart attacks, strokes. Reduces the risk of blood clot formation in at-risk individuals.

iv) **Anti-Inflammatory Use :** Treatment for rheumatoid arthritis, osteoarthritis, and gout.

➢ Side Effects of Aspirin

While aspirin is highly effective, it may cause adverse effects, particularly with long-term use—

i) **Gastrointestinal Issues :** Gastric ulcers, bleeding, and irritation. Increased risk of gastritis with prolonged use.

ii) **Bleeding Tendencies :** Increased risk of bleeding disorders and hemorrhage.

iii) **Tinnitus and Hearing Loss :** High doses may lead to ringing in the ears (tinnitus).

iv) **Allergic Reactions :** Skin rashes, asthma exacerbation (aspirin-sensitive asthma)

3.10 Comparison with Other Analgesic & Antipyretic Drugs

Drug	Type	Fever Reduction	Pain Relief	Anti-inflammatory	Major Side Effects
Paracetamol	Analgesic/ Antipyretic	High	Moderate	Low	Liver toxicity (overdose)
Ibuprofen	NSAID	High	Strong	Strong	Gastric irritation, kidney damage
Aspirin	NSAID	High	Strong	Strong	Gastric ulcers, bleeding, Reye's syndrome

3.11 Summary

➢ Analgesics relieve pain without altering consciousness. Analgesics are mainly two types—

i) **Opioid (Narcotic) Analgesics :** Act on CNS, high addiction risk (e.g., Morphine, Codeine).

ii) **Non-Opioid (Non-Narcotic) Analgesics/NSAIDs :** Reduce inflammation (e.g., Aspirin, Paracetamol, Ibuprofen).

➢ Anti-Inflammatory Agents acts by inhibiting COX enzymes (COX-1, COX-2).

➢ Antipyretic Agents are used to lower fever by acting on the hypothalamus by inhibiting prostaglandin E_2 (PEG_2) synthesis.

➢ Ibuprofen, a NSAID, pain reliever, fever reducer that Inhibits COX-1 and COX-2, reducing prostaglandins.

➢ Paracetamol (Acetaminophen) is mild analgesic & antipyretic Irreversibly inhibits COX-1 & COX-2.

3.12 Exercises

A. Multiple Choice Questions (MCQs)

1. Which starting material is used in the synthesis of aspirin?
   a) Acetic acid
   b) Salicylic acid
   c) p-Aminophenol
   d) Isobutylbenzene

Answer : b) Salicylic acid

2. What is the main byproduct in the synthesis of paracetamol?
   a) Hydrochloric acid
   b) Acetic acid
   c) Carbon dioxide
   d) Sulfuric acid

Answer : b) Acetic acid

3. Which reagent is used for the oxidation step in ibuprofen synthesis?
   a) Zinc dust
   b) Acetic anhydride
   c) Chromic acid
   d) Sodium hydroxide

Answer : c) Chromic acid

4. Which enzyme is primarily inhibited by NSAIDs?
   a) Phospholipase A_2
   b) Cyclooxygenase (COX)
   c) Lipoxygenase
   d) Caspase

Answer : b) Cyclooxygenase (COX)

5. Which of the following is a selective COX-2 inhibitor?
   a) Ibuprofen
   b) Naproxen

c) Celecoxib

d) Aspirin

Answer : c) Celecoxib

6. Which of the following is a non-opioid analgesic?

a) Morphine

b) Codeine

c) Ibuprofen

d) Fentanyl

Answer : c) Ibuprofen

7. What is the major side effect of prolonged NSAID use?

a) Addiction

b) Respiratory depression

c) Gastrointestinal ulcers

d) Euphoria

Answer : c) Gastrointestinal ulcers

8. Which enzyme is inhibited by most antipyretics?

a) Lipoxygenase

b) Cyclooxygenase (COX)

c) Amylase

d) Phospholipase

Answer : b) Cyclooxygenase (COX)

9. Which of the following is a commonly used antipyretic drug?

a) Morphine

b]) Paracetamol

c) Lidocaine

d) Metformin

Answer : b) Paracetamol

B. Short Answer Questions

1. Describe the acetylation reaction involved in the synthesis of aspirin.
2. What role does p-aminophenol play in paracetamol synthesis?
3. Explain the importance of the Friedel-Crafts acylation reaction in ibuprofen synthesis.

4. Differentiate between steroidal and non-steroidal anti-inflammatory drugs.
5. Describe the mechanism of action of NSAIDs.
6. Explain the mechanism of action of opioid analgesics.
7. Describe the acetylation reaction in aspirin synthesis.
8. Describe the mechanism of action of antipyretic agents.
9. Why is paracetamol considered safer than other NSAIDs?
10. List three common side effects of NSAIDs.

C. Long Answer Questions

1. Compare and contrast the synthesis of aspirin and paracetamol in terms of reagents and mechanism.
2. Outline the stepwise synthesis of ibuprofen and discuss its significance as an NSAID.
3. Explain the role of COX enzymes in inflammation and how NSAIDs modulate their activity.
4. Compare and contrast opioid and non-opioid analgesics in terms of mechanism and side effects.
5. Discuss the clinical uses and risks associated with paracetamol overdose.
6. Explain the differences between NSAIDs and selective COX-2 inhibitors as antipyretics.
7. Discuss the role of natural antipyretics in fever management.
8. What precautions should be taken while using antipyretic drugs?

Unit 4 : Antibiotics

4.0 Objectives

By the end of this unit, students should be able to—

- Understand the Concept of Antibiotics, define antibiotics and explain their role in treating bacterial infections.
- Describe Chloramphenicol, understand its chemical structure, classification, and mechanism of action.
- Identify the broad-spectrum activity of chloramphenicol and its clinical applications.
- Explain how bacterial resistance to chloramphenicol develops and its impact on clinical use.

4.1 Introduction

Antibiotics are chemical substances that inhibit or kill bacterial growth, playing a crucial role in the treatment of infectious diseases. Among them, chloramphenicol is a broad-spectrum antibiotic with significant clinical importance. Discovered in 1947, it was the first antibiotic to be synthesized artificially, making it widely available for medical use. Due to its effectiveness against a wide range of Gram-positive

and Gram-negative bacteria, it is used to treat severe infections like typhoid fever, meningitis, and respiratory tract infections. Here we will learn about antibiotics specially chloramphenicol.

4.2 Antibiotics

Many micro-organisms produce among themselves chemical substances which when extracted interfere with the growth or metabolism of other micro-organism. Such compounds are known as, **"antibiotics"**. An antibiotic is therefore defining as follow—

- It is a chemical substance produced by or derived from living cells which is capable in small concentration to inhibit the life processes or even destroying some other micro-organisms. Antibiotics are required in very low concentration to bring about their therapeutic action and so they are also sometimes termed as, Chemotherapeutics agents. All chemical substances produced by or derived from living cells are however cannot be antibiotics, they have to satisfy certain conditions in order to be designated as antibiotics.

In order for a particular antibiotic to act as therapeutic agent, it should have to satisfies the following conditions—

a) Effective Against Pathogens: It must be able to fight against harmful microorganisms.

b) Low Toxicity: It should not cause significant side effects in the host.

c) High Stability: It must be stable enough to be isolated and processed into forms that can be easily absorbed by the body.

d) Long Shelf Life: It should be able to be stored for a long time without losing its effectiveness.

e) Controlled Elimination: The body should detoxify and eliminate the drug at a rate that allows enough time between doses, while maintaining a proper concentration level.

f) Complete Clearance: Once treatment stops, the antibiotic should be completely eliminated from the body.

[**Chemotherapeutic drugs :** are harmful to invading bacteria, virus but harmless to the host.]

4.3. History of Antibiotics

Antibiotics are medicines used to fight bacterial infections. The first antibiotic, **Penicillin,** was discovered by **Alexander Fleming** in 1928. In the 1940s, antibiotics

became widely available and helped save millions of lives. Over time, new antibiotics have been developed to fight different types of bacterial infections.

4.4 Classification of antibiotics

Antibiotics include a wide range of compounds with different chemical structures, making their classification complex. Various classification methods have been proposed, which are as follows—

i) Classification Based on Spectrum of Activity

a) Broad-Spectrum Antibiotics : These antibiotics are effective against a wide range of bacteria and can treat multiple infections. While they overlap in effectiveness, each is particularly useful for certain diseases. **Examples :** Penicillin, Chloramphenicol, Tetracyclines.

b) Narrow-Spectrum Antibiotics : These antibiotics target specific bacterial strains and have a highly selective action. **Examples :** Bacitracin, Nystatin.

ii) Classification Based on Bacterial Strains (Gram-Positive & Gram-Negative)

This method classifies antibiotics based on their ability to kill **Gram-positive** or **Gram-negative bacteria,** determined through Gram staining. In gram staining process a bacterial smear is treated with crystal violet dye, followed by iodine. It is then washed with alcohol. Bacteria that retain the violet color are Gram-positive. Bacteria that lose the violet color and absorb a red counterstain (safranin) are Gram-negative.

a) Gram-Positive Antibiotics : Effective against Gram-positive bacteria like *Diphtheria bacillus, Leprosy bacillus, Pneumococcus, Staphylococcus, Streptococcus, Tubercle bacillus.* **Examples :** Penicillin, Vancomycin.

b) Gram-Negative Antibiotics : Effective against Gram-negative bacteria like *E. coli, Typhoid bacillus, Gonococcus, Meningococcus, Plague bacillus, Helicobacter pylori.* **Examples :** Streptomycin, Polymyxins.

iii) Classification Based on Chemical Structure & Therapeutic Use

This classification of antibiotics is based on their chemical structures or therapeutic actions, although here exists great variations in the structural moieties of antibiotics yet there are certain similarities in their structure as well and it has been observed that such structurally similar antibiotics exert their therapeutic action also in a similar manner. These different classes are—

a) Penicillin : these are derived from amino acids, e.g. Cephalosporin.

b) **Chloramphenicol & Its Synthetic Analogues :** Act by inhibiting bacterial protein synthesis.

c) **Aminoglycoside :** They usually contain a sugar molecule glycoside alkali linked to amino compound. e.g. Streptomycin, Vancomycin etc.

d) **Tetracyclines :** the content four 6-membered fused ring system.

e) **Macrolides :** discounted a large lactone ring. e.g.- Erythromycin.

f) **Lincomycin :** these are S containing antibiotics in which S atom is not present in a ring.

g) **Polypeptide :** they contain 6-12 amino acid residues and they include some very potent bactericident antibiotics. e.g.-Bracitracin.

h) **Antineoplastic antibiotics :** these groups of antibiotics are used to control cancer. e.g.- Mitomycin.

i) **Antitubercular antibiotic :** these are a group of drugs used to treat tuberculosis e.g., Rifampin, Isoniazid, Pyrazinamide, and Ethambutol

j) **Polyacetylene antibiotics :** this compound in addition of acyclic bonds also contain ethylene bond with another functional group. They are usually very toxic and have limited application.

k) **Unclassified antibiotics :** this includes a number of antibiotics which not related to any one the classes described above.

4.5. Uses of Antibiotics

- Treating Bacterial Infections: Antibiotics are used for infections like pneumonia, tuberculosis, and strep throat.
- Preventing Infections: Doctors prescribe antibiotics before surgeries to prevent infections.
- Agriculture: Some antibiotics are used in livestock to prevent diseases.

4.6 Antibiotic Resistance

Antibiotic resistance occurs when bacteria develop the ability to defeat the drugs meant to kill them.

- **Causes of Antibiotic Resistance**
  1. Overuse of antibiotics.
  2. Not completing the full course of antibiotics.
  3. Using antibiotics for viral infections.
  4. Poor infection control in hospitals.

➢ Effects of Antibiotic Resistance

- Common infections become harder to treat.
- Patients need stronger and more expensive medicines.
- Increases the risk of spreading resistant bacteria.

➢ How to Prevent Antibiotic Resistance

- Use antibiotics only when prescribed.
- Complete the full course of treatment.
- Avoid using antibiotics for viral infections like colds and flu.
- Maintain good hygiene to prevent infections.

4.7. Side Effects of Antibiotics

While antibiotics are useful, they can have side effects, including—

- **Mild Side Effects :** Nausea, diarrhea, stomach pain.
- **Severe Side Effects :** Allergic reactions, liver damage, kidney problems.

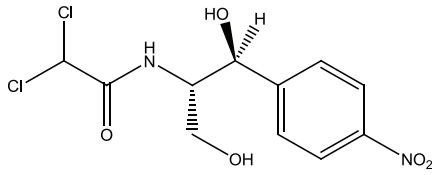
It is important to use antibiotics correctly to minimize side effects and avoid resistance.

4.8 Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic isolated from *Streptomyces Venezuelae.* It is a levorotatory compound. It has a nitrobenzene moiety that is responsible for antibacterial activity and the bitter taste. It is the first natural product found to contain a $–NO_2$ group. Chloramphenicol has a wide range activity that induces gram-positive, gram-negative, aerobic and anaerobic bacteria. It is very effective in the treatment typhoid fever and in some other bacterial infections which are insensitive to other antibacterial agents.

➢ Structure of Chloramphenicol

Chloramphenicol has two possible pair of enantiomers only the levorotatory isomer is the biologically active isomer.

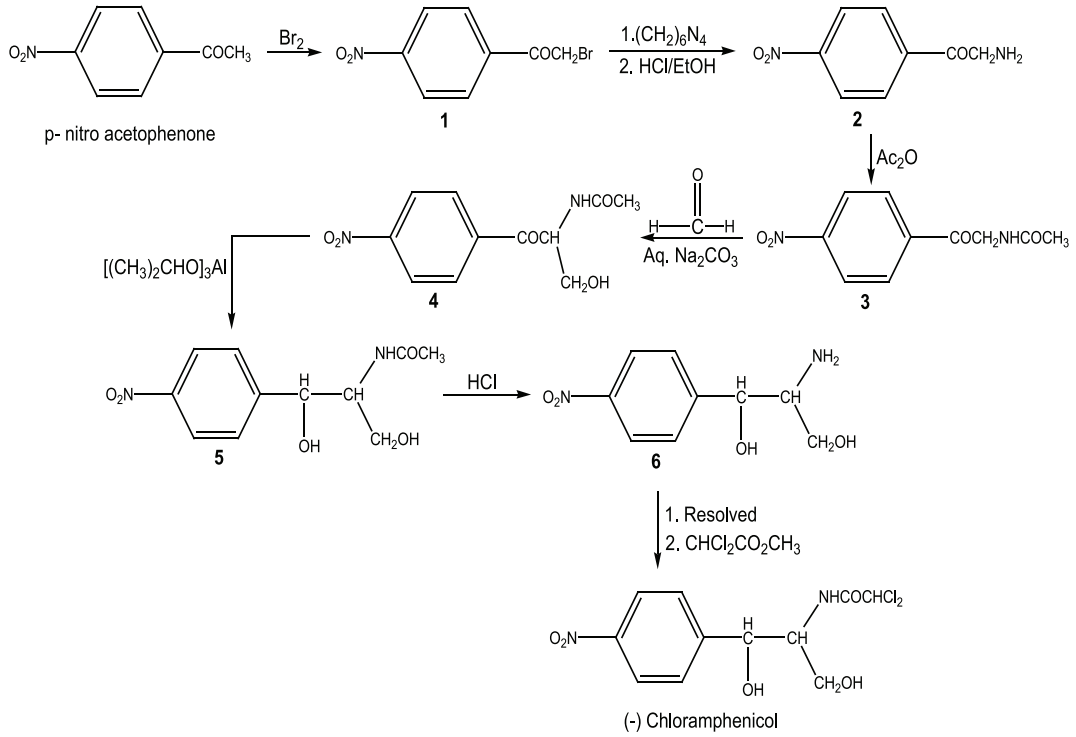


2,2-dichloro-N-[(1R, 2R)-1,3-dihydroxy-1-(4-nitrophenyl)propane-2-yl]acetamide

➢ Mechanism of action of Chloramphenicol

Chloramphenicol is a bacteriostatic by inhibiting protein synthesis. It prevents protein chain elongation by inhibiting the peptidyl transferase activity of the bacterial ribosome. It inhibits protein synthesis by binding to 50s ribosomal subunit of the microbe. This action stops bacterial growth and prevents them from multiplying.

➢ Synthesis of Chloramphenicol



Reduction of **4** with $[(CH_3)_2CHO]_3Al$ (Aluminiumisopropoxide) get predominantly the threo isomer of **5** together with a small amount of its erythro isomer, this are separated by fractional crystallization. Compound **6** is obtained as a mixture of (±) form is resolved by (+)Champhor sulfonic acid, the D(-)erythro isomer of 6 was then converted to (-)Chloramphenicol on treatment with methyl dichloro acetate.

➢ Uses of Chloramphenicol

- Treatment of typhoid fever caused by *Salmonella typhi*.
- Bacterial meningitis caused by Haemophilus influenzae and Neisseria meningitidis.
- Eye infections (used as eye drops or ointments).
- Treatment of anaerobic bacterial infections.

➢ Side Effects of Chloramphenicol

- Bone marrow suppression, leading to aplastic anemia (a rare but serious condition).
- Gray baby syndrome in newborns (due to immature liver enzymes unable to metabolize the drug properly).
- Gastrointestinal disturbances such as nausea, vomiting, and diarrhea.

➢ Precautions for use of Chloramphenicol

- Should only be used when no safer alternatives are available due to its severe side effects.
- Avoid prolonged use to prevent toxic effects.
- Regular blood tests are recommended for patients on long-term therapy.

4.9 Summary

- ➢ Antibiotics are chemical substances produced by or derived from living organisms that inhibit or destroy other microorganisms.
- ➢ They work in small concentrations and are also known as chemotherapeutic agents.
- ➢ Penicillin, the first antibiotic, was discovered by Alexander Fleming in 1928.
- ➢ Antibiotic Resistance occurs when bacteria develop resistance to antibiotics, making treatment difficult.
- ➢ Chloramphenicol which is a Broad-Spectrum Antibiotic, isolated from Streptomyces venezuelae. Effective against: Gram-positive, Gram-negative, aerobic, and anaerobic bacteria.
- ➢ Chloramphenicol commonly used for typhoid fever and bacterial infections resistant to other antibiotics.
- ➢ Chloramphenicol inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit.
- ➢ Prevents protein chain elongation, stopping bacterial growth.

4.10 Exercises

A. Multiple Choice Questions (MCQs)

1. Which of the following is a broad-spectrum antibiotic?
   a) Penicillin G
   b) Tetracycline

c) Vancomycin
d) Rifampin

Answers : b

2. Antibiotic resistance occurs due to:
   a) Overuse of antibiotics
   b) Not completing the full course
   c) Using antibiotics for viral infections
   d) All of the above

Answers : d

3. Which antibiotic inhibits protein synthesis?
   a) Penicillin
   b) Tetracycline
   c) Rifampin
   d) Polymyxins

Answers : b

4. Which of the following is a broad-spectrum antibiotic?
   a) Penicillin G
   b) Tetracycline
   c) Vancomycin
   d) Rifampin

Answers : b

5. Which serious condition is treated with Chloramphenicol ?
   a) typhoid fever
   b) Kidney failure
   c) Hypertension
   d) Diabetes

Answers : a

B. Short Answer Questions

1. What are antibiotics and how do they work?
2. Who discovered the first antibiotic, and what was it called?
3. What is the difference between broad-spectrum and narrow-spectrum antibiotics?
4. What are the causes of antibiotic resistance?
5. Explain the mechanism of action of Chloramphenicol.
6. What are the major side effects of Chloramphenicol?

Unit 5 : Antibacterial, Antifungal and Antiviral Agents

5.0 Objectives

After studying this unit, learners will be able to—

- Explain the classification of antibacterial, antifungal, and antiviral agents.
- Understand the chemical structure and therapeutic uses of sulphonamides, Sulphanethoxazole, Sulphacetamide, and Trimethoprim.
- Define antifungal agents and their significance in treating fungal infections.
- Explain the role of Acyclovir in treating viral infections, especially Herpes Simplex Virus (HSV).
- Identify common side effects, contraindications, and drug interactions.

5.1 Introduction

Infectious diseases caused by bacteria, fungi, and viruses have been a major challenge to human health for centuries. The discovery and development of antimi-

crobial agents have revolutionized medicine, enabling effective treatment and prevention of life-threatening infections. This unit explores three major categories of antimicrobial agents: antibacterial, antifungal, and antiviral drugs. This chapter will discuss these essential antimicrobial agents, their mechanisms of action, clinical uses, side effects, and challenges, including the growing concern of drug resistance.

5.2 Antibacterial agents

Antibacterial agents are a group of materials that fight against pathogenic bacteria by killing or reducing the metabolic activity of bacteria, their pathogenic effect in the biological environments will be minimized. To cure infectious diseases, researchers discovered antibacterial agents, which are considered to be the most promising chemotherapeutic agents. The antibacterial agents can be classified into four major groups—(i) Type of action, (ii) Source, (iii) Spectrum of activity, (iv) Chemical structure

5.2.1 Classification based on the type of action

Generally, antibacterial agents can be classified on the basis of type of action i.e. "bacteriostatic and bactericidal". Antibacterials, those that slow or inhibit the growth of bacteria are called, bacteriostatic and the antibacterials, which destroy bacteria by targeting the cell wall or cell membrane of the bacteria, are referred to as bactericidal. The inhibition of phenomenon of bacteriostatic agents involves inhibition of protein synthesis or some bacterial metabolic pathways. Since, bacteriostatic agents just prevent the growth of the pathogenic bacteria, sometimes it is very difficult to a clear distinction between bacteriostatic and bactericidal, and especially when high concentrations of some bacteriostatic agents are used then they may work as bactericidal. Hence, Antibacterial agents are classified as—

- **Bacteriostatic :** Inhibit bacterial growth (e.g., Sulphonamides, Trimethoprim, Chloramphenicol)
- **Bactericidal :** Kill bacteria by targeting their cell walls or DNA (e.g., Penicillins, Cephalosporins, Quinolones)

Examples of bacteriostatic and bactericidal antibacterial along with their mode of action are presented in following table—

1. Bacteriostatic antibacterial	**Function**
Sulphonamides	They act to inhibit folate synthesis at initial stages
Amphenicols, e.g. Chloramphenicol	They inhibit protein synthesis

Spectinomycin	It binds to the 30S ribosomal subunit, thereby interrupting protein synthesis
Trimethoprim	It disturbs the tetrahydrofolate synthesis pathway
2. Bactericidal antibacterial	**Function**
Penicillins, Oxacillin, Cloxacillin and Flucloxacillin. They belong to β-lactams antibiotic class	Penicillin antibiotics stop bacteria from multiplying by preventing bacteria from forming the walls that surround them. The walls are necessary to protect the bacteria from their environment, and to keep the contents of the bacterial cell together. Bacteria cannot survive without a cell wall. This class of antibiotics also used to treat skin infections, external ear infections, infections of leg ulcers, diabetic foot infections, and infection of bone.
Carbapenems like Imipenem, Meropenem, Aztreonam, Tricaracillinclvulnate, and Piperaciintazobactam- these are β-lactam inhibitors. Some others β- lactam inhibitors are cephalosporin, e.g.- Cefotaxime, Ceftriaxone and Cefepime.	They interfering the synthesis of the bacterial cell wall
Gentamicin, Tobramycin and Amikacin are aminoglycosides	They inhibit protein synthesis
Quinolones and Flouroquinolones such as Levofloxacin, Ciprofloxacin and Oxifloxacin	They block bacterial DNA replication

5.2.2 Classification based on source of antibacterial agents

Antibacterial agents can be naturally obtained from fungal sources, semi- synthetic members which are chemically altered natural product or synthetic. Antibacterials are the subclass of antibiotics. Cephalosporins, Benzylpenicillin and Gentamicin are well- known examples of natural antibiotics/antibacterials. Natural antibacterial often exhibits higher toxicity than synthetic antibacterials. Ampicillin and Amikacin are semi-synthetic antibiotics, which were developed to show lower toxicity and increase effectiveness. Synthetic antibiotics are also designed to have even greater effectiveness and less toxicity and have an advantage over the natural antibiotics that the bacteria are not exposed to the compounds until they are released. Thus classification Based on Sourceof the antibacterial agents are—

- **Natural :** Derived from microorganisms (e.g., Penicillins, Cephalosporins, Gentamicin)
- **Semi-Synthetic :** Chemically modified for better efficacy (e.g., Ampicillin, Amikacin)
- **Synthetic :** Fully manufactured in labs (e.g., Quinolones)

5.2.3 Classification based on spectrum of activity

This classification based on their (antibacterial agents) target specification. In this category, the antibacterials may be either narrow or broad spectrum. The narrow spectrum antibacterials are considered to be those which can work on a narrow range of microorganism, i.e. they act against gram-positive and gram-negative bacteria only. Usually, the narrow spectrum antibacterials are considered ideal antibacterial and preferred over the broad spectrum antibacterials, because the narrow spectrum antibiotics do not kill as many of the normal microorganism in the body as the broad-spectrum antibiotics and thus has less ability to cause superinfection. Also, the narrow spectrum antibiotic will cause less resistance of the bacteria as it will ideal with only specific bacteria. We can conclude the classification as follows.

- **Narrow Spectrum :** Target specific bacteria (e.g., *Penicillin G*)
- **Broad Spectrum :** Effective against multiple bacterial types (e.g., Tetracyclines, Fluoroquinolones)

5.2.4 Classification based on chemical structure

Different skeleton containing antibiotics show different therapeutic behavior; therefore, it is an ultimate need to classify antibacterials on the basis of their chemical structure. This classification is also very important as similar structural units have similar structural units have similar patterns of toxicity, effectiveness and other related properties. On the structural basis, antibacterials have been classified into two groups: group A (β- lactams) and group B (aminoglycoside). However, in a more elaborated way, the antibacterial can be classified into β-lactams, β-lactam/β-lactamase inhibitor combinations, aminoglycoside, macrolides, quinolones and flouroquinolones.

5.3 Antifungal agents

Most fungal infections (mycoses) involve superficial invasion of the skin or mucous membrane of the body orifices. These diseases, which can usually be controlled by local application of antifungal agents. Mycoses are classified into two main types based on their cause—

i) **Dermatophyte Infections :** The Dermatophytes are contagious superficial epidermal infections caused by various Epidermophyton, Microsporum and Trichophyton species.

ii) **Yeast & Mold Infections :** Mycoses caused by pathogenic saprophytic yeasts (Aspergillus, Blastomyces, Candida, Cryptococcus and Histoplasma), which are contagious and usually superficial infections involving the skin and mucous membranes. Under certain conditions, these are capable of invading deeper body cavities and causing systematic mycoses. Such infections may become serious and occasionally life-threatening. Moreover, they are difficult to treat.

➢ Classification of Antifungal agents

Antifungal drugs work by targeting different components of fungal cells. Summary of Major Classes are summarized below.

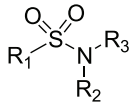
Class	Mechanism of Action	Examples	Uses
Polyenes	Bind to ergosterol, create pores in cell membrane	Amphotericin B, Nystatin	Systemic & superficial infections
Azoles	Inhibit ergosterol synthesis	Fluconazole, Ketoconazole, Clotrimazole	Broad-spectrum antifungals
Echinocandins	Inhibit β-glucan (cell wall synthesis)	Caspofungin, Micafungin	Candida, Aspergillus
Pyrimidine Analogues	Inhibit DNA/RNA synthesis	Flucytosine (5-FC)	Cryptococcal meningitis
Allylamines	Inhibit squalene epoxidase (ergosterol synthesis)	Terbinafine, Naftifine	Skin and nail infections
Mitotic Inhibitors	Inhibit microtubules & mitosis	Griseofulvin	Dermatophyte nfections

5.4 Sulphonamides

Sulphonamides are synthetic, broad spectrum bacteriostatic antibiotics. The sulphonamide drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and are of bacterial infections in human beings. These are totally synthetic substances that are produced by relatively simple chemical synthesis. Because of associated toxicity and high rates of resistance, their use is now very limited. The sulphonamide-antibacterials are primarily used for the

treatment of uncomplicated urinary tract infections caused by E.coli, Enterobacter and proteus and only seldom for middle ear infections caused by *Haemophilus influenzae.* Sulphonamides are also used for the prophylaxis of recurrent rheumatic fever associated with streptococcal infection and are also useful in burn therapy.

➢ Structure of Sulphonamides



Basic structure of sulphonamides

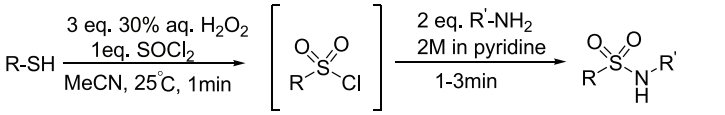
(R_1, R_2, and R_3 can be alkyl, aryl and heteroaryl)

➢ Synthesis of Sulphonamides

The classic approach of synthesis of sulphonamides, is the reaction of sulphonyl chlorides with an amine. The reaction of primary and secondary amines with benzenesulphonyl chloride is the basis of Hinsberg reaction, a method for detecting primary and secondary amines.

$$RSO_2Cl + R_2NH \rightarrow RSO_2NR_2 + HCl$$

The combination of H_2O_2 and $SOCl_2$ is a highly reactive agent for the direct oxidative conversion of thiol derivatives to the corresponding sulphonyl chlorides through oxidative chlorination. Upon reaction with amines, the corresponding sulphonamides were obtained in excellent yields in very short reaction times.



R= Ar, alkyl, Bn

R'= Ar, alkyl

➲ Key facts about Sulphonamides

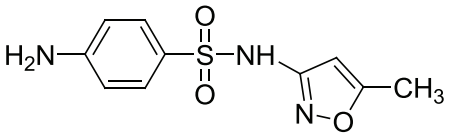
- ♦ **Sulphonamides** were the **first antibacterial drugs,** widely used in infections.
- ♦ Though their use is now **limited due to resistance,** they are still essential for **UTIs, respiratory infections, and burn care.**
- ♦ **Combination therapy** (e.g., **Co-trimoxazole**) helps overcome bacterial resistance and improve effectiveness.

5.5 Sulphamethoxazole

Sulphamethoxazole is a bacteriostatic antibiotic- interferes with folic acid synthesis insusceptible bacteria. It is generally given in combination with trimethoprim, which inhibits a sequential step in bacterial folic acid synthesis—these agent works synergistically to block two consecutive steps in the biosynthesis of nucleic acids and proteins which are necessary for bacterial growth and division, and using

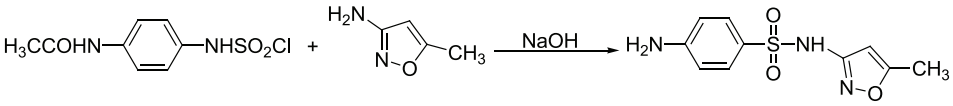
them in conjunction helps to slow the development of bacterial resistant. In this combination, sulphamethoxazole is useful for the treatment of a variety of bacterial infections, including those of the urinary, respiratory and gastrointestinal tracts.

➢ Structure of Sulphamethoxazole



4-amino-N-(5-methyl-1,2-oxazol-3-yl)benzene-1-sulphonamide

➢ Synthesis of Sulphamethoxazole



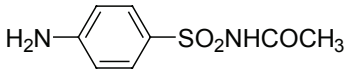
➲ Key facts about Sulphamethoxazole

- ♦ **Sulphamethoxazole** is a widely used sulphonamide antibiotic that inhibits folic acid synthesis in bacteria.
- ♦ Proper hydration is essential to prevent kidney-related complications.

5.6. Sulphacetamide

An anti-infective agent that is used to treat skin infections and orally urinary tract infections. Sulphacetamide is asulphonamide antibiotic with bacteriostatic actions and broad spectrum activity against most gram-positive and many gram-negative organisms. Most of the sulphonamides are readily absorbed orally. However, parenteral administration is difficult, since the soluble sulphonamides salts are highly alkaline and irritating to the tissues. The sulphonamides are widely distributed throughout all tissues. High levels are achieved in pleural, peritoneal, synovial and ocular fluids. Although these drugs are no longer used to treat meningitis, CFS levels are high in meningeal infections. Their antibacterial action is inhibited by pus.

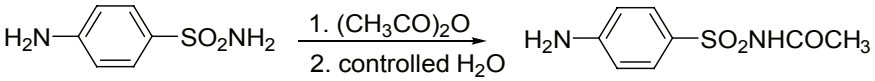
➢ Structure of Sulphacetamide



N-(4-aminobenzenesulphonyl)acetamide

➢ Synthesis of Sulphacetamide

Sulphacetamide is synthesized by reacting 4-aminobenzenesulphonamide with acetic anhydride under controlled hydrolysis.



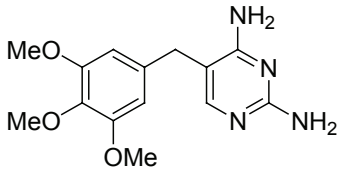
➢ Key facts about Sulphacetamide

- ♦ Sulphamethoxazole is a widely used sulphonamide antibiotic that inhibits folic acidsynthesis in bacteria.
- ♦ Drink lots of water to prevent kidney-related complications.

5.7. Trimethoprim

Trimethoprim is an antifolate antibacterial agent – inhibits bacterial dihydrofolate reductase (DHFR), a critical enzyme that catalyzes the formation of tetrahydrofolic acid (THF)—in doing so, it prevents the synthesis of bacterial DNA and ultimately continued bacterial survival. Trimethoprim is often used in combination with sulphamethoxazole due to their complementary and synergistic mechanisms but may be used as a monotherapy in the treatment and/or prophylaxis of urinary tract infections. It is structurally and chemically related to pyrimethamine, another antifolate antimicrobial used in the treatment of plasmodial infections.

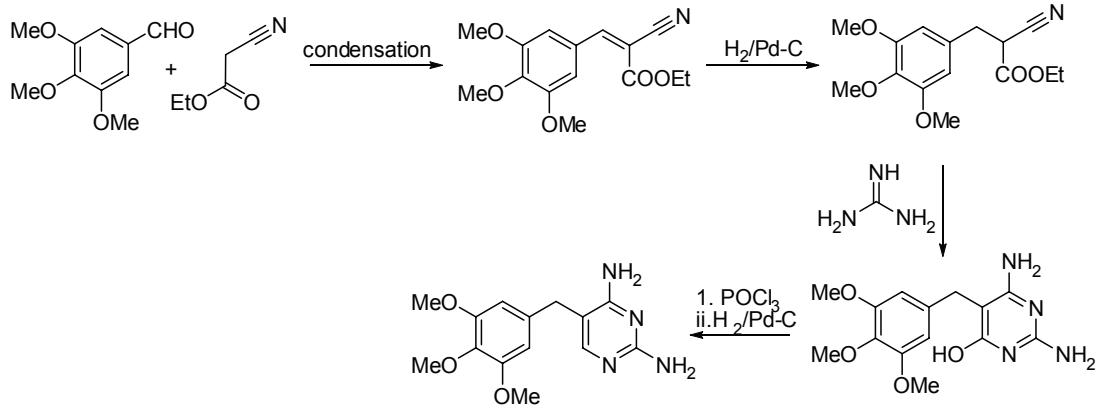
➢ Structure of Trimethoprim



5-[(3,4,5-trimethoxyphenyl)methyl]pyrimidine-2,4-diamine

➢ Synthesis of Trimethoprim

Trimethoprim is synthesized form 3,4,5-trimethoxybenzaldehyde. Condensation of 3,4,5-trimethoxybenzaldehyde with 3-ethoxy or 3-anilinopropionitrile gives the corresponding benzylidene derivative, which upon direct reaction with guanidine gives trimethoprim.



➢ Key facts about Trimethoprim

- ♦ Trimethoprim is a bacteriostatic antifolate antibiotic used mainly for UTIs, respiratory infections, and gastrointestinal infections.
- ♦ It works by inhibiting bacterial dihydrofolate reductase (DHFR), preventing DNA synthesis.
- ♦ Patients on long-term therapy should take folic acid supplements to prevent anemia.
- ♦ Not safe during pregnancy due to risk of fetal folic acid deficiency.

5.8 Antiviral agents

Antiviral agents are a class of medication used specifically for treating or controlling viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike antibiotics, which kill bacteria, antiviral drugs specifically target viruses without harming human cells.

➢ Mechanism of Action of Antiviral Agents

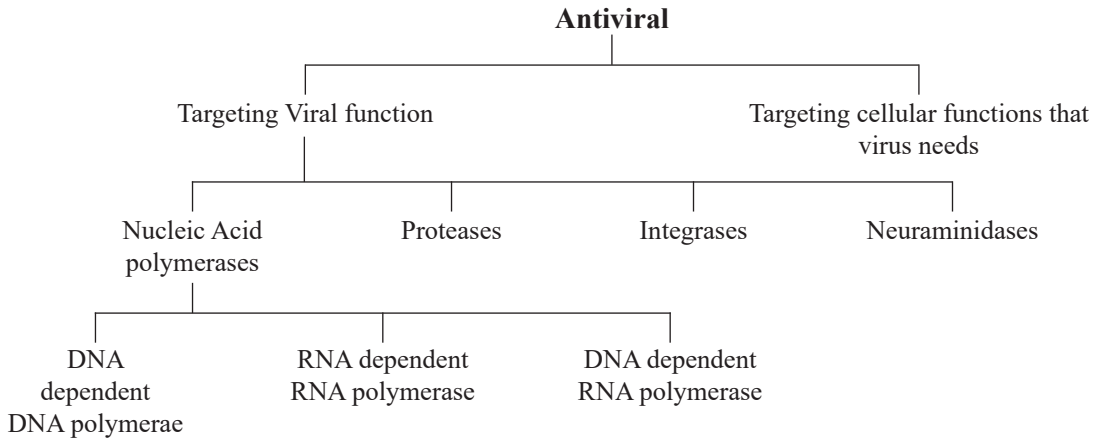
Antiviral drugs work in different ways, including—

- ■ Preventing virus entry into host cells.
- ■ Blocking viral replication by inhibiting enzymes needed for virus multiplication.
- ■ Preventing virus release from infected cells, stopping its spread.
- ■ Boosting the immune system to help fight the infection.

➢ Types of Antiviral Drugs

Antiviral agents are classified based on the type of virus they target—

- ■ **Anti-Herpes Drugs :** Used for infections like herpes simplex and chickenpox. Example: Acyclovir, Valacyclovir
- ■ **Anti-Influenza Drugs :** Treat flu infections. Example: Oseltamivir (Tamiflu), Zanamivir
- ■ **Anti-HIV Drugs (Antiretrovirals) :** Used for HIV/AIDS treatment. Example: Zidovudine, Tenofovir, Efavirenz
- ■ **Anti-Hepatitis Drugs :** Used for hepatitis B and C infections. Example: Ribavirin, Lamivudine, Sofosbuvir
- ■ **Broad-Spectrum Antivirals :** Effective against multiple viruses. Example: Remdesivir (used for COVID-19)



Classification of the Antiviral drugs based on their targets

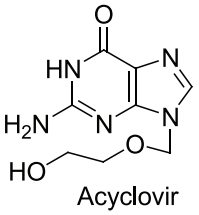
➢ Limitations of Antiviral Drugs

- Viruses mutate quickly, making some antivirals less effective over time.
- They do not cure viral infections but help control symptoms and reduce viral load.
- Some antivirals have side effects such as nausea, headaches, or liver toxicity.

5.9 Acyclovir (an Antiviral agents)

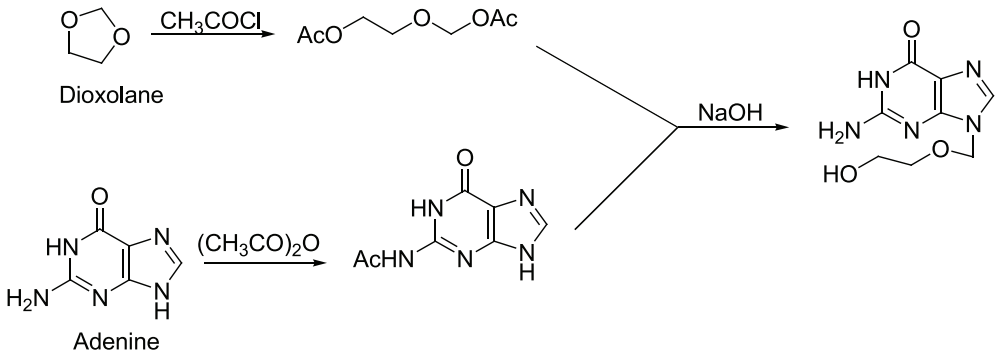
Acyclovir is an antiviral medication. Acyclovir is used to treat infections caused by certain types of viruses. It treats cold sores around the mouth (caused by herpes simplex), shingles (caused by herpes zoster) and chickenpox. This medication is also used to treat outbreaks of genital herpes. The viruses that cause these infections continue to live in the body even between outbreaks. Acyclovir decreases the severity and length of these outbreaks. It helps the sores heal faster, keeps new sores from forming and decreases pain/ itching. This medication may also help reduce how long pain remains after the sores heal. In addition, in people with a weakened immune system, acyclovir can decrease the risk of the virus spreading to other parts of the body and causing serious infections.

➢ Structure of Acyclovir



Acyclovir

➢ **Synthesis of Acyclovir**



➢ **Uses of Acyclovir**

- ♦ Treats cold sores (HSV-1) and genital herpes (HSV-2).
- ♦ Reduces severity and duration of chickenpox & shingles (VZV).
- ♦ Prevents herpes outbreaks in immunocompromised patients (e.g., HIV/AIDS, cancer).

➢ **Side Effects of Acyclovir**

- ■ Nausea, vomiting, headache, dizziness
- ■ Kidney toxicity (especially with IV use)
- ■ Rare neurological effects (hallucinations, confusion)

Antibacterial agents fight bacterial infections by inhibiting or killing bacteria.

5.10. Summary

➢ Antibacterial agents fight bacterial infections by inhibiting or killing bacteria. Bacteriostatic: Inhibit bacterial growth (e.g., Sulphonamides, Trimethoprim). Bactericidal: Kill bacteria by targeting cell walls or DNA (e.g., Penicillins, Quinolones).

➢ Sulphonamides, First synthetic antibacterial drugs, now limited due to resistance. Used for UTIs, respiratory infections, and burn therapy. Work by inhibiting folic acid synthesis in bacteria.

➢ Sulphamethoxazole, Bacteriostatic antibiotic, interferes with folic acid synthesis. Used in combination with Trimethoprim to prevent resistance.

➢ Sulphacetamide, Broad-spectrum sulphonamide used for skin and urinary tract infections. Well-distributed in body tissues but inhibited by pus.

- Trimethoprim, Antifolate antibacterial, blocks bacterial DNA synthesis. Used alone or with Sulphamethoxazole for UTIs, respiratory, and GI infections.
- Antiviral Agents, work by blocking virus entry, replication, or release.
- Acyclovir is an Antiviral Agent, used for herpes infections (HSV-1, HSV-2), chickenpox, and shingles. Reduces outbreak severity and duration.

5.11 Exercises

A. Multiple Choice Questions (MCQs)

1. Sulphonamides act by inhibiting:
   a) Protein synthesis
   b) Folic acid synthesis
   c) Cell wall synthesis
   d) DNA replication
2. Which of the following is used to treat eye infections?
   a) Sulphamethoxazole
   b) Sulphacetamide
   c) Trimethoprim
   d) Acyclovir
3. Acyclovir is mainly used to treat:
   a) Bacterial infections
   b) Fungal infections
   c) Viral infections
   d) Parasitic infections

Answers : 1—b, 2—b, 3—c

B. Short Answer Questions

1. What are antifungal agents?
2. Name any two broad-spectrum antifungal drugs.
3. What are sulphonamides? Give two examples.
4. How does trimethoprim work against bacterial infections?
5. Name one antifungal drug and its use.
6. What is the mechanism of action of Acyclovir?
7. Why is it important to complete the full course of antibiotics?

Unit 6 : Central Nervous System agents

6.0 Objectives

By the end of this chapter, students should be able to:

- Identify the classification of CNS depressants, particularly barbiturates and benzodiazepines.
- Describe the clinical applications of Phenobarbital and Diazepam in managing conditions such as epilepsy, anxiety, and insomnia.
- Recognize the common side effects, toxicity, and contraindications associated with these drugs.

6.1 Introduction

The central nervous system (CNS) plays a crucial role in regulating bodily functions, emotions, and cognition. Various disorders, such as epilepsy, anxiety, and insomnia, require pharmacological intervention using CNS agents. Among these, Phenobarbital and Diazepam are widely used drugs with significant therapeutic applications. This chapter will provide a comprehensive understanding of how these agents influence the central nervous system and their role in therapeutic management.

6.2 Central Nervous System (CNS) agents

The central nervous system consists of the brain and spinal cord. The brain plays a central role in the control of most bodily functions, including awareness, move-

ments, sensations, thoughts, speech and memory. Some reflex movements can occur via spinal cord pathways without the participation of brain structures. Drugs works on CNS, including anesthetics, anticonvulsants, antimetics, antiparkinson agents, CNS stimulants, muscle relaxants, pain relievers, nonnarcotic analgesics (such as actamiophen and NSAIDs) and sedatives.

6.3 Classification of CNS Agents

CNS agents can be broadly classified into the following categories—

1. **CNS Stimulants (Drugs that increase brain activity)**

   These drugs increase alertness, wakefulness, and energy levels. They are used to treat conditions like ADHD (Attention Deficit Hyperactivity Disorder), narcolepsy, and depression. Examples: Caffeine, Amphetamines (e.g., Methylphenidate), Modafinil

2. **CNS Depressants (Drugs that slow brain activity)**

   These drugs reduce anxiety, induce sleep, and calm the nervous system. They are used for insomnia, anxiety, and seizures. Examples: Barbiturates (e.g., Phenobarbital), Benzodiazepines (e.g., Diazepam, Lorazepam)

3. **Antipsychotic Agents (Drugs for mental disorders)**

   These drugs are used to treat psychotic disorders like schizophrenia and bipolar disorder. They help control hallucinations, delusions, and mood swings. Examples: Haloperidol, Clozapine, Risperidone

4. **Antidepressants (Drugs for depression and anxiety disorders)**

   These drugs improve mood, reduce stress, and help treat depression and anxiety disorders. Examples: Fluoxetine, Sertraline, Amitriptyline, Phenelzine

5. **Antiepileptic Drugs (Drugs for seizures)**

   These drugs help control seizures (fits) by stabilizing nerve activity in the brain. Examples: Phenytoin, Carbamazepine, Valproic acid

6. **Anti-Parkinson's Drugs (Drugs for movement disorders)**

   These drugs are used to treat Parkinson's disease, which affects movement and coordination. Examples: Levodopa, Carbidopa, Ropinirole

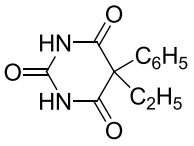
7. **Anesthetics (Drugs for pain relief and unconsciousness)**

   Anesthetics are used during surgery to block pain and induce unconsciousness. Examples: Lidocaine, Procaine, Propofol, Halothane

6.4 Phenobarbital

Phenobarbital is a prescription medicine used to treat and prevent the symptoms of seizures, sedation, hypnotics, Insomina and Status Epilepticus. Phenobarbital may be used alone or with other medications. Phenobarbital belongs to a class of drugs called Anticonvulsants, Barbiturates.

➢ Structure of Phenobarbital



Phenobarbital

➢ Synthesis of Phenobarbital

Barbiturate drugs are obtained via condensation reactions between a derivative of diethylmalonate and urea in the presence of a strong base. The methods consist of a Pinner reaction of benzyl cyanide, giving phenylacetic acid ethyl ester. Subsequently, this ester undergoes cross claisen condensation using diethyl oxalate, giving diethyl ester of phenyloxobutandioic acid. Upon heating this intermediate easily loses carbon monoxide, yielding diethyl phenylmalonate. Malonic ester synthesis using ethyl bromide leads to the formation of α-phenyl-α-ethylmalonic ester. Finally a condensation reaction with urea produced phenobarbital.

➢ Uses of Phenobarbital

- ♦ Treatment of epilepsy (generalized and focal seizures)
- ♦ Sedation for anxiety and insomnia
- ♦ Management of withdrawal symptoms in alcohol dependence

➢ Side Effects of Phenobarbital

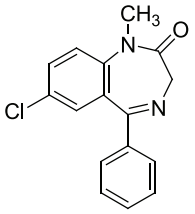
- ■ Drowsiness
- ■ Dizziness
- ■ Respiratory depression (at high doses)
- ■ Dependency with prolonged use

6.5 Diazepam

Diazepam is used to treat anxiety, alcohol withdrawal and seizures. It is also used to relieve muscle spasms and to provide sedation before medical procedures. This

medication works by claiming the brain and nerves. Diazepam belongs to a class of drugs known as benzodiazepines.

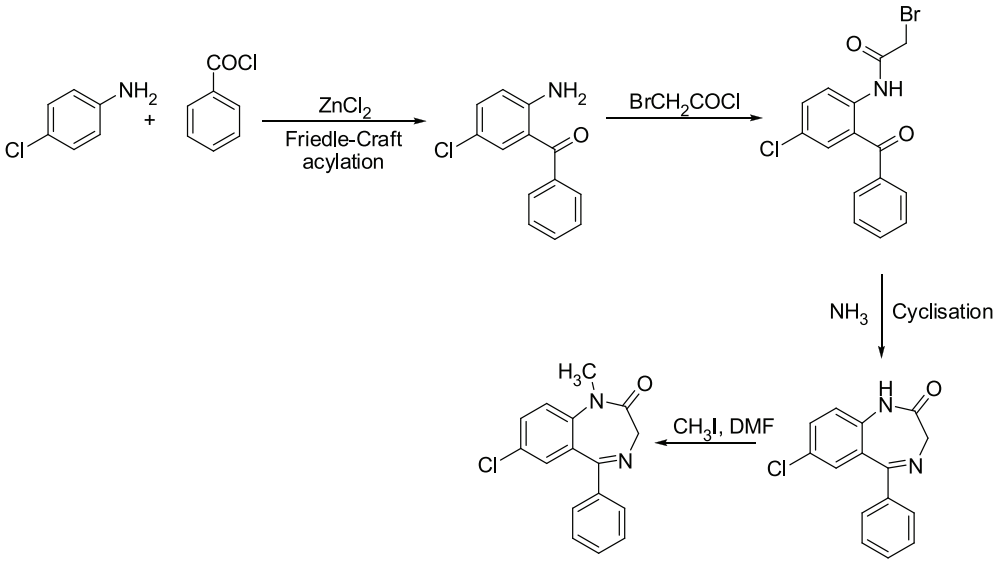
➢ Structure of Diazepam



Diazepam

(7-Chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one)

➢ Synthesis of Diazepam



➲ Uses of Diazepam

- ♦ Treatment of anxiety disorders
- ♦ Management of muscle spasms
- ♦ Control of seizures and status epilepticus
- ♦ Alcohol withdrawal symptom relief

➢ Side Effects of Diazepam

- ■ Drowsiness
- ■ Fatigue
- ■ Muscle weakness
- ■ Dependency and withdrawal symptoms with prolonged use

6.6 Summary

- Drugs affecting the CNS include anesthetics, anticonvulsants, antiemetics, antiparkinsonian agents, CNS stimulants, muscle relaxants, analgesics (e.g., acetaminophen, NSAIDs), and sedatives.
- Phenobarbital is used in treating epilepsy (both generalized and focal seizures), providing sedation for anxiety and insomnia, and managing alcohol withdrawal symptoms.
- Side effects of Phenobarbital may include drowsiness, dizziness, respiratory depression (at high doses), and potential dependency with prolonged use.
- Diazepam is utilized for treating anxiety disorders, managing muscle spasms, controlling seizures and status epilepticus, and alleviating alcohol withdrawal symptoms.
- Side Effects of Diazepam can cause drowsiness, fatigue, muscle weakness, and may lead to dependency and withdrawal symptoms with extended use.

6.7 Exercises

A. Multiple Choice Questions (MCQs)

1. Which of the following is a CNS stimulant?
   a) Diazepam
   b) Methylphenidate
   c) Haloperidol
   d) Carbamazepine

Answer : b

2. Antiepileptic drugs are used to treat:
   a) Depression
   b) Seizures
   c) Anxiety
   d) Parkinson's disease

Answer : b

3. Which drug is used as a local anesthetic?
   a) Propofol
   b) Halothane
   c) Lidocaine
   d) Levodopa

Answer : c

B. Short Answer Questions

1. What are CNS agents? Name two examples.
2. Differentiate between CNS stimulants and CNS depressants.
3. What are CNS agents, and how are they classified?
4. Explain the mechanism of action of Phenobarbital.
5. List three major uses of Phenobarbital.
6. What are the potential side effects of Phenobarbital?
7. Describe the mechanism of action of Diazepam.
8. What are the common uses of Diazepam?
9. List the possible side effects of Diazepam.

Unit 7 : Cardiovascular and Anti Leprosy Agent

7.0 Objective

By the end of this chapter, students should be able to:

- Describe Cardiovascular and antilaprosy agent
- Describe the clinical uses of Glyceryl Trinitrate in managing cardiovascular conditions such as angina pectoris, and the role of Dapsone in treating leprosy and other dermatological conditions.
- Identify common side effects, potential toxicities, and contraindications associated with both Glyceryl Trinitrate and Dapsone.
- Discuss the considerations for the safe and effective use of these medications, including patient education and monitoring requirements.

7.1 Introduction

The cardiovascular and antilaprosy agents, Glyceryl Trinitrate and Dapsone, play pivotal roles in the management of cardiovascular diseases and leprosy, respectively. This chapter delves into the pharmacological properties, therapeutic applications, adverse effects, and clinical considerations associated with glyceryl trinitrate and dapsone. A comprehensive understanding of these agents is essential for their effective and safe use in clinical practice.

7.2 Drugs for Cardiovascular disease

Relating to the circulatory system, which comprises the heart and blood vessels and carries nutrients and oxygen to the tissues of the body and removes carbon dioxide

and other wastes from them. Cardiovascular diseases are conditions that affect the heart and blood vessels and include arteriosclerosis, coronary artery disease, heart value disease, arrhythmia, heart failure, hypertension, shock, endocarditis and congenital heart disease. Medications for cardiovascular diseases help regulate heart function, blood pressure, and cholesterol levels.

7.3 Classification of Cardiovascular Drugs

Cardiovascular drugs are classified based on their mechanism of action and therapeutic use. Below is a general classification:

i) **Anti-Hypertensive Drugs (For High Blood Pressure) :** Lower blood pressure. **Example :** Beta-blockers (Atenolol, Metoprolol), ACE inhibitors (Enalapril, Lisinopril), Calcium channel blockers (Amlodipine, Verapamil)

ii) **Diuretics :** Help remove excess fluid and reduce blood pressure. **Example :** Thiazide diuretics (Hydrochlorothiazide), Loop diuretics (Furosemide), Potassium-sparing diuretics (Spironolactone)

iii) **Anti-Anginal Drugs (For Chest Pain) :** Improve blood supply to the heart. **Example :** Nitrates (Nitroglycerin), Beta-blockers (Propranolol), Calcium channel blockers (Diltiazem)

iv) **Anticoagulants and Antiplatelet Drugs :** Prevent blood clot formation. **Example :** Warfarin, Heparin, Aspirin, Clopidogrel

v) **Anti-Hyperlipidemic Drugs (Lipid-Lowering Drugs) :** Reduce cholesterol levels. **Example :** Statins (Atorvastatin, Simvastatin), Fibrates (Fenofibrate)

vi) **Anti-Arrhythmic Drugs (For Irregular Heart Rhythms) :** Help regulate heart rhythm. **Example :** Amiodarone, Digoxin

vii) **Anti-Heart Failure Drugs :** Improve heart function. **Example :** Digoxin, Beta-blockers, ACE inhibitors

7.4 Glyceryl Trinitrate

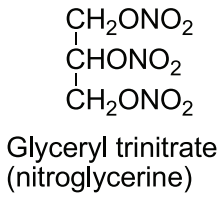
Nitroglycerin, also known as glyceryl trinitrate, is a medication used for heart failure, high blood pressure, anal fissures, and painful periods and to treat and prevent chest pain caused by decreased blood flow to the heart or due to the recreational use of cocaine.It belongs to the class of nitrate vasodilators, which help in relaxing and widening blood vessels to improve blood circulation.

➢ Mechanism of Action

GTN works by releasing nitric oxide (NO) in the body. Nitric oxide activates an enzyme called guanylate cyclase, which increases the levels of cyclic guanosine monophosphate (cGMP). This leads to:

1. Relaxation of vascular smooth muscles
2. Dilation of coronary arteries, increasing oxygen supply to the heart
3. Reduced preload and afterload, which decreases the heart's workload and oxygen demand

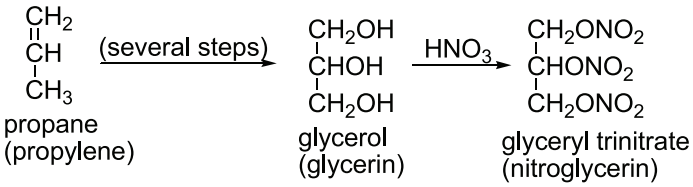
➢ Structure of Glyceryl Trinitrate



Glyceryl trinitrate
(nitroglycerine)

➢ Synthesis of Glyceryl Trinitrate

Glyceryl trinitrate, is synthesized by nitrating glycerol with nitric acid.



propane (propylene) | glycerol (glycerin) | glyceryl trinitrate (nitroglycerin)

➢ Uses of Glyceryl Trinitrate

- ♦ Treatment of angina pectoris
- ♦ Management of heart failure (in acute conditions)
- ♦ Controlling blood pressure during surgeries
- ♦ Treatment of hypertensive emergencies

➢ Side Effects of Glyceryl Trinitrate

Common side effects of GTN include—

- ■ Headache (due to vasodilation)
- ■ Dizziness and lightheadedness
- ■ Low blood pressure (hypotension)
- ■ Flushing of the skin
- ■ Reflex tachycardia (increase in heart rate)

➢ Precautions & Contraindications for the use of Glyceryl Trinitrate

- GTN should not be used with phosphodiesterase inhibitors (e.g., Sildenafil-Viagra) as it can cause severe hypotension.
- Patients with severe anemia, glaucoma, or head trauma should use it cautiously.
- Long-term use can lead to nitrate tolerance, reducing its effectiveness.

7.5 Drugs for Anti-Leprosy

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae*. It mainly affects the skin, peripheral nerves, mucosa of the upper respiratory tract, and eyes. The disease progresses slowly, and if left untreated, it can cause permanent disabilities.

To treat leprosy effectively and prevent drug resistance, the World Health Organization (WHO) recommends Multi-Drug Therapy (MDT), which includes a combination of—

- Dapsone (Bacteriostatic, prevents bacterial growth)
- Rifampicin (Highly bactericidal, kills M. leprae quickly)
- Clofazimine (Anti-inflammatory, prevents leprosy reactions)

MDT is free in many countries including India through WHO programs. It helps to prevent drug resistance & transmission of Leprosy. Early diagnosis and adherence to MDT can cure leprosy completely.

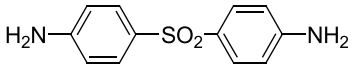
7.6 Dapsone

Dapsone, also known as diaminodiphenyl sulfone (DDS), is used for the treatment of infection caused by *Mycobacterium leprae*. It is used in the treatment of both lepromatous and tuberculoid types of leprosy. Dapsone is used in combination with Rifampicin and Clofazimine. Dapsone is also the drug of choice for dermatitis herpetiformis, with pyrimethamine for the treatment of malaria, with trimethoprim for pneumocystis carnii and has been used for rheumatoid arthritis.

➢ Mechanism of Action of Dapsone

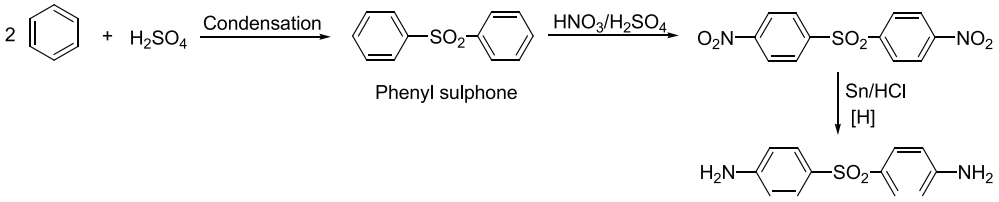
- Dapsone inhibits the enzyme dihydropteroate synthase, which is essential for folic acid synthesis in bacteria.
- This prevents bacterial DNA replication, ultimately stopping bacterial growth (bacteriostatic action)

➢ Structure of Dapsone



Dapsone
(4,4'-sulphonyl bis benzenamine)

➢ Synthesis of Dapsone



➢ Uses of Dapsone

- ♦ Used as first-line drug in combination therapy to treat Leprosy (Hansen's disease)
- ♦ Used to treat a chronic skin condition associated with gluten sensitivity.
- ♦ Used in skin diseases

➢ Side Effects of Dapsone

- ■ Hemolysis
- ■ Skin rash,
- ■ Nausea, vomiting, and abdominal pain.
- ■ Headache and dizziness.

7.7 Summary

- ➢ Glyceryl Trinitrate acts as a vasodilator by releasing nitric oxide, leading to relaxation of vascular smooth muscles, dilation of coronary arteries, and reduced cardiac workload.
- ➢ Adverse Effects of Glyceryl Trinitrate include headaches, dizziness, hypotension, flushing, and reflex tachycardia.
- ➢ Dapsone is used to treat leprosy
- ➢ Dapsone Inhibits dihydropteroate synthase, disrupting folic acid synthesis in bacteria, thereby exerting a bacteriostatic effect.
- ➢ Potential side effects of Dapsone include hemolysis, particularly in individuals with G6PD deficiency, skin rashes, gastrointestinal disturbances, and peripheral neuropathy.

7.8 Exercises

1. What is the primary mechanism of action of Glyceryl Trinitrate?
2. Name two medical conditions where GTN is used.
3. List two common side effects of GTN.
4. Explain how GTN reduces the workload of the heart.
5. What is the mechanism of action of Dapsone?
6. What are the major uses of Dapsone?
7. List the common side effects of Dapsone.
8. How is Dapsone used in the treatment of leprosy?
9. What is the Multi-Drug Therapy (MDT)

MCQs Question

1. Which of the following is NOT a cardiovascular disease?
   A) Arteriosclerosis
   B) Coronary artery disease
   C) Endocarditis
   D) Tuberculosis

Answer : D) Tuberculosis

2. Which class of drugs is used to lower blood pressure?
   A) Anti-anginal drugs
   B) Anti-hypertensive drugs
   C) Anti-hyperlipidemic drugs
   D) Anti-coagulants

Answer : B) Anti-hypertensive drugs

3. What is the primary function of anti-anginal drugs?
   A) Lower cholesterol levels
   B) Improve blood supply to the heart
   C) Prevent blood clot formation
   D) Reduce irregular heartbeats

Answer : B) Improve blood supply to the heart

4. What is the mechanism of action of Glyceryl Trinitrate (GTN)?
   A) Inhibits sodium-potassium pump
   B) Blocks calcium channels

C) Releases nitric oxide, leading to vasodilation

D) Stimulates beta receptors

Answer : C) Releases nitric oxide, leading to vasodilation

5. Why should Glyceryl Trinitrate NOT be used with Sildenafil (Viagra)?

A) It can cause severe hypotension

B) It increases blood pressure

C) It reduces drug absorption

D) It leads to arrhythmia

Answer : A) It can cause severe hypotension

6. Which drug is NOT used in anti-leprosy treatment?

A) Rifampicin

B) Dapsone

C) Clofazimine

D) Metoprolol

Answer : D) Metoprolol

7. What is the mechanism of action of Dapsone?

A) Inhibits folic acid synthesis

B) Blocks calcium channels

C) Lowers cholesterol levels

D) Prevents blood clotting

Answer : A) Inhibits folic acid synthesis

8. Which of the following is NOT a therapeutic use of Glyceryl Trinitrate?

A) Treatment of angina

B) Management of heart failure

C) Blood pressure control during surgeries

D) Treatment of diabetes

Answer : D) Treatment of diabetes

Unit 8 : HIV-AIDS related drugs

8.0 Objectives

By the end of this chapter, readers should be able to:

- Understand how HIV-AIDS related drugs e.g. Zidovudine inhibits HIV replication and its role in the management of HIV/AIDS.
- Recognize the primary indications for Zidovudine, including its use in combination antiretroviral therapy for HIV treatment and prevention of mother-to-child transmission.
- Be aware of common and serious side effects associated with Zidovudine, such as headaches, gastrointestinal disturbances, hematologic toxicity, and potential for lactic acidosis.

8.1 Introduction

This chapter aims to provide an in-depth exploration of HIV-AIDS related drugs taking an example of Zidovudine, covering its pharmacological properties, thera-

peutic applications, synthesis, and potential adverse effects. A comprehensive understanding of this drug is essential for healthcare professionals involved in the management of HIV/AIDS, as it informs effective treatment strategies and enhances patient care.

8.2 Anti-HIV agents

Acquired immune deficiency syndrome (AIDS) is caused by the retrovirus, HIV. The HIV infection that targets the lymphocytes, the monocytes and macrophages expressing the surface CD-4 receptors, eventually produces profound defects in cell-mediated immunity. Overtime infection leads to severe depletion of CD-4 T-lymphocytes resulting in opportunistic infection like tuberculosis, fungal, viral, protozoal and neoplastic diseases and ultimately death.

The development of Antiretroviral Therapy (ART) has transformed HIV/AIDS from a fatal disease into a manageable chronic condition. ART does not cure HIV but helps in suppressing viral replication, maintaining immune function, and reducing the risk of transmission.

8.3 Key Classes of Anti-HIV Agents

HIV (Human Immunodeficiency Virus) is treated with Antiretroviral Therapy (ART), which includes a combination of drugs from different classes to effectively suppress the virus and prevent resistance. The major classes of anti-HIV drugs are:

8.3.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs inhibit the reverse transcriptase enzyme, which HIV uses to convert its RNA into DNA. These drugs mimic natural nucleotides (building blocks of DNA), get incorporated into the growing viral DNA chain, and terminate the chain prematurely, halting HIV replication.

- **Common Drugs**
  - Zidovudine (AZT)
  - Lamivudine (3TC)
  - Abacavir (ABC)
  - Tenofovir (TDF/TAF)
- **Use**

NRTIs are often used as part of combination therapy to reduce viral load. They are foundational in the treatment of HIV, especially when combined with other antiretrovirals to prevent drug resistance.

8.3.2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs bind directly to the reverse transcriptase enzyme and inhibit its function. Unlike NRTIs, NNRTIs do not mimic the building blocks of DNA. Instead, they bind to a specific site on the enzyme, altering its shape and preventing it from converting viral RNA into DNA.

- **Common Drugs**
  - Efavirenz (EFV)
  - Nevirapine (NVP)
  - Etravirine (ETV)
- **Use**

NNRTIs are commonly used in combination regimens, but resistance can develop quickly if used alone. They are typically used in first-line HIV therapy due to their potency, though some newer options (like Dolutegravir) are replacing them for better efficacy and fewer side effects.

8.3.3. Protease Inhibitors (PIs)

Protease inhibitors target the protease enzyme, which HIV needs to process long viral proteins into smaller, functional pieces. By inhibiting protease, these drugs prevent the virus from assembling and releasing mature, infectious virus particles.

- **Common Drugs**
  - Lopinavir (LPV)
  - Ritonavir (RTV)
  - Darunavir (DRV)
  - Atazanavir (ATV)
- **Use**

Protease inhibitors are potent, but they are often used in combination with a pharmacokinetic enhancer (like Ritonavir) to boost their effectiveness. PIs are used in second-line or more advanced treatment regimens when other drugs fail or when patients develop resistance.

8.3.4. Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs prevent the integrase enzyme from integrating HIV's genetic material into the host cell's DNA. Without this integration, the viral DNA cannot be replicated or transcribed into new virus particles.

➢ **Common Drugs**

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Bictegravir (BIC)

➢ **Use**

INSTIs are highly potent and have a low risk of drug resistance, making them preferred in first-line treatment regimens. They are often used in combination with other drugs to provide maximal viral suppression.

8.3.5. Entry Inhibitors (Fusion Inhibitors and CCR_5 Antagonists)

Entry inhibitors prevent HIV from entering human cells. Fusion inhibitors block the virus's ability to fuse with the cell membrane, while CCR_5 antagonists block the CCR_5 receptor on the surface of immune cells, preventing HIV from attaching and entering the cell.

➢ **Common Drugs**

- Maraviroc (MVC) (CCR_5 antagonist)
- Enfuvirtide (T-20) (fusion inhibitor)

➢ **Use**

Entry inhibitors are usually reserved for treatment-experienced patients with multidrug-resistant HIV or those who have failed other therapies. They are not typically used in first-line therapy but offer an important option for complex cases.

8.4 Role of healthcare providers in managing HIV/AIDS treatment

Healthcare providers play a crucial role in managing HIV/AIDS treatment by ensuring effective care, improving patient outcomes, and preventing transmission. Their responsibilities encompass various aspects, including medical treatment, patient education, emotional support, and public health initiatives.

i) **Diagnosing and Initiating Treatment :** Early and accurate diagnosis of HIV through screening and confirmatory tests. Educating patients about their condition and available treatment options. Initiating antiretroviral therapy (ART) promptly to suppress viral replication and boost immune function.

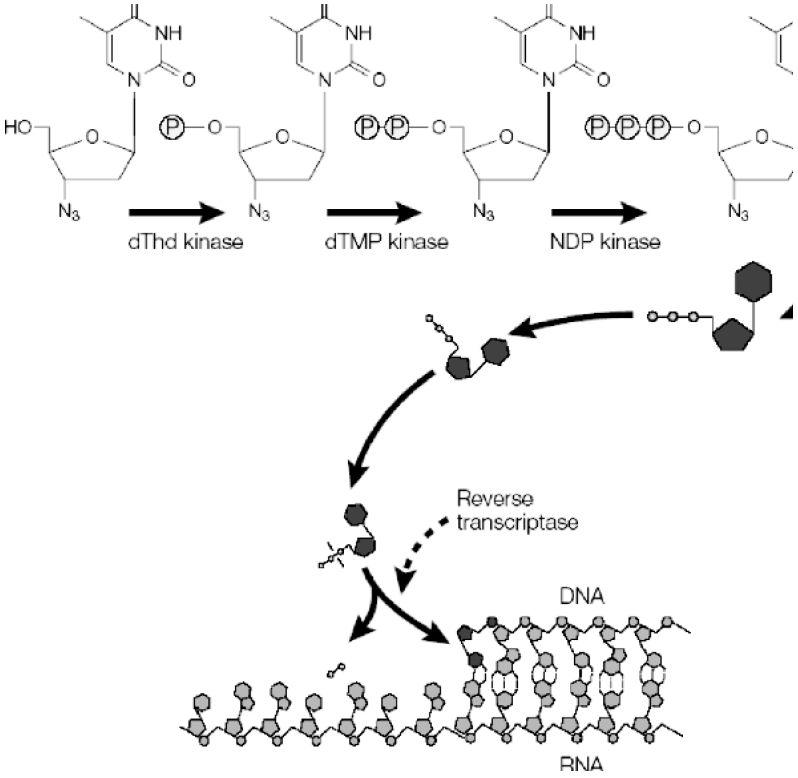
ii) **Monitoring and Managing Treatment :** Managing co-infections (e.g., tuberculosis, hepatitis) and comorbidities like cardiovascular diseases or mental health issues.

iii) **Providing Counseling and Support :** Educating patients on adherence to ART, lifestyle modifications, and risk reduction strategies.

iv) **Preventing Transmission :** Encouraging safe sex practices and the use of pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for high-risk individuals.

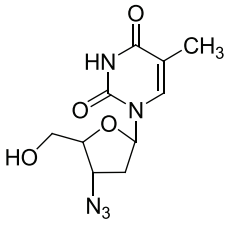
8.5. Zidovudine (or AZT)

Zidovudine, also known as Azidothymidine (AZT), is a nucleoside derivative of reverse transcriptase inhibitors and an antiretroviral medication used to prevent and treat HIV/AIDS. AZT is only active against HIV. When the virus is replicating into proviral DNA (viral DNA synthesized prior to integration into host DNA). This is because the active compound AZT, has a high affinity for an enzyme called, reverse transcriptase, which is used by HIV to replicate viral single-stranded RNA into proviral double-stranded DNA. AZT contains a N_3 group in place of the usual nucleoside -OH group. As a result, reverse transcriptase incorporates AZT into growing strands of HIV proviral DNA and DNA synthesis and replication are terminated (see following figure), since subsequent nucleoside cannot bind to the nitrogen group of AZT.



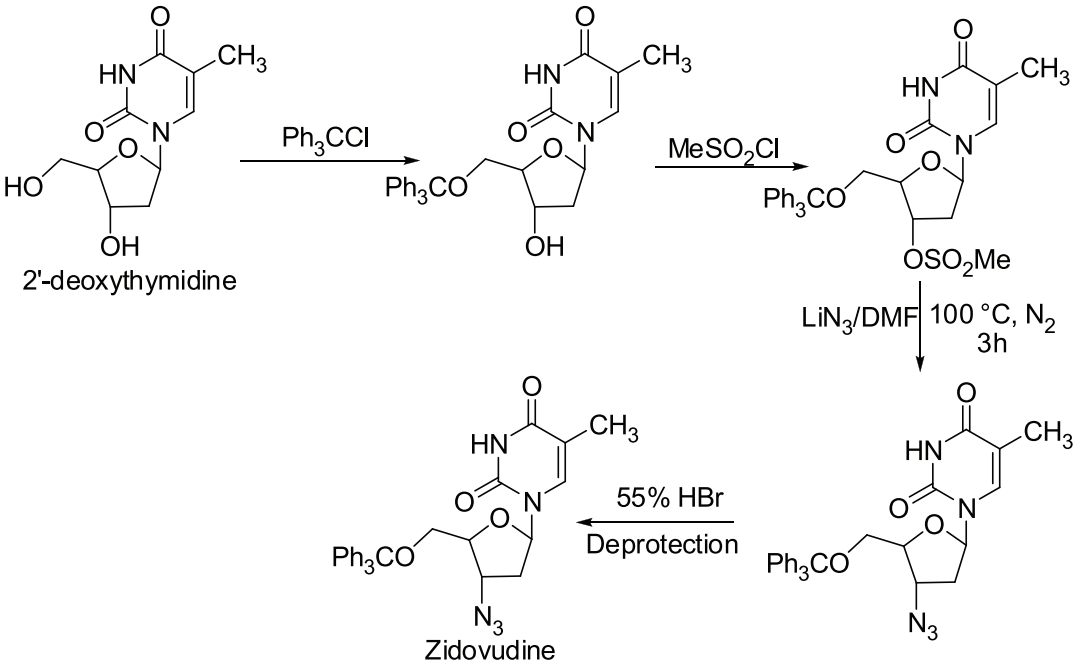
It is generally recommended for use with other anti-retrovirals. It may be used to prevent mother-to-child spread during birth or after a needle stick injury or other potential exposure. It is sold both by itself and together as Lamivudine/Zidovudine and Abacavir/Lamivudine/Zidovudine. It can be used by mouth or by slow injection into vein. Common side effects include headaches, fever and nausea. Serious side effects include liver problems, muscle damage and high blood lactate levels. It is commonly used in pregnancy and appears to be safe for the baby.

➢ Structure of Zidovudine



Zidovudine

➢ Synthesis of Zidovudine



➢ Mechanism of Action of Zidovudine

Zidovudine works by mimicking one of the natural building blocks of DNA. It is converted into its active form, Zidovudine triphosphate, by cellular enzymes. Once incorporated into the viral DNA during replication, Zidovudine terminates

the DNA chain, preventing further viral replication. This halts the virus from proliferating, reducing the viral load in the body.

As an NRTI, Zidovudine selectively inhibits the reverse transcriptase enzyme, which is critical for HIV's ability to replicate inside human cells. Since human DNA polymerase (the enzyme that copies human DNA) is not affected, Zidovudine specifically targets HIV's replication process with minimal damage to the host cell.

➢ Use of Zidovudine

- ♦ HIV Infection: Zidovudine is primarily used to treat HIV infection in combination with other antiretroviral agents. It is not used alone due to the risk of resistance.
- ♦ Prevention of HIV Transmission: Zidovudine is also used to prevent the transmission of HIV from an HIV-positive mother to her baby during childbirth (perinatal transmission).
- ♦ Post-exposure Prophylaxis (PEP): In some cases, it can be used as part of the post-exposure prophylaxis regimen for individuals who have been exposed to HIV (e.g., healthcare workers following a needle stick injury).

➢ Side Effects of Zidovudine

While Zidovudine has been a cornerstone of HIV treatment, it can cause a variety of side effects such as

- ■ Gastrointestinal: Nausea, vomiting, loss of appetite, and diarrhea.
- ■ Fatigue: This is one of the most common side effects.
- ■ Headache: Occasional headaches may occur with treatment.

➢ Resistance of Zidovudine

- ■ As with all antiretroviral drugs, resistance can develop when Zidovudine is used alone or inappropriately. HIV can mutate to become resistant to Zidovudine, leading to treatment failure. This is why combination therapy is essential in HIV treatment, using a mix of drugs from different classes to prevent resistance.
- ■ Resistance to Zidovudine usually occurs through mutations in the reverse transcriptase gene of the virus, which make the enzyme less sensitive to inhibition by the drug.

8.6 Summary

- ➢ Acquired Immune Deficiency Syndrome (AIDS): AIDS is caused by the Human Immunodeficiency Virus (HIV).

- HIV infection leads to a significant decline in cell-mediated immunity, making individuals susceptible to opportunistic infections such as tuberculosis, fungal, viral, protozoal infections, and certain cancers.
- HIV treatment involves a combination of drugs from different classes to effectively suppress the virus and prevent resistance. The major classes include—i) Nucleoside Reverse Transcriptase Inhibitors (NRTIs), ii) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), iii) Protease Inhibitors (PIs), iv) Integrase Strand Transfer Inhibitors (INSTIs) and v) Entry Inhibitors
- Zidovudine, also known as Azidothymidine (AZT), is a nucleoside reverse transcriptase inhibitor (NRTI) used to prevent and treat HIV/AIDS.
- HIV can develop resistance to AZT through mutations in the reverse transcriptase gene, underscoring the importance of combination therapy to prevent treatment failure.

8.7 Exercises

Section A : Multiple Choice Questions (MCQs)

1. Which of the following drugs is a Nucleoside Reverse Transcriptase Inhibitor (NRTI)?
   a) Efavirenz
   b) Zidovudine
   c) Darunavir
   d) Raltegravir

Answer : b) Zidovudine

2. Which class of drugs is commonly used in pre-exposure prophylaxis (PrEP)?
   a) Protease Inhibitors
   b) Integrase Strand Transfer Inhibitors
   c) Nucleoside Reverse Transcriptase Inhibitors
   d) Non-Nucleoside Reverse Transcriptase Inhibitors

Answer : c) Nucleoside Reverse Transcriptase Inhibitors

3. What is the primary purpose of Antiretroviral Therapy (ART)?
   a) To cure HIV
   b) To reduce HIV viral load

c) To prevent the transmission of HIV

d) To prevent AIDS

Answer : b) To reduce HIV viral load

4. Which of the following is an example of a Protease Inhibitor?

a) Tenofovir

b) Lopinavir

c) Dolutegravir

d) Maraviroc

Answer : b) Lopinavir

Section B : Short Answer Questions

1. Name three protease inhibitors used for HIV.
2. Describe the role of combination therapy in HIV treatment.
3. Discuss the role of healthcare providers in managing HIV/AIDS treatment.
4. Describe two common side effects of HIV/AIDS medications and suggest possible solutions for managing them.

Section C : Long Answer Questions

1. Discuss the different classes of drugs used in HIV treatment. Include examples from each class and explain their mechanisms of action. Discuss the significance of combination therapy in managing HIV.
2. Describe the impact of drug resistance in HIV treatment. How does drug resistance develop, and what strategies can be employed to manage or prevent it?
3. Discuss the current challenges in the management of HIV/AIDS treatment. Focus on issues such as adherence, side effects, resistance, and access to medications, and suggest possible solutions to these challenges.

Unit 9 : Fermentation

9.0 Objectives

In this unit fermentation process was elaborately discussed and, in this section, also different features of fermentation process for preparing antibiotics, amino acids, vitamins were demonstrated. The objective of this chapter is to provide a comprehensive understanding of aerobic and anaerobic fermentation processes and their industrial applications in the production of various compounds. End of this chapter model questions will also involve actively all learners.

9.1 Introduction

Fermentation is the chemical transformation of organic substances into simple compounds by the action of enzymes, complex organic catalysts, which are produced by the microorganism such as molds, yeasts or bacteria. This process converts sugar to acids, gases or alcohol. In fermentation molecules such as glucose are broken down anaerobically. More broadly, in food production it is the foaming that occurs during the manufacture of wine and beer. In biochemistry, it is narrowly defined as the extraction of energy from carbohydrates in the absence of oxygen. Humans have used fermentation to produce foodstuffs and beverages since the Neolithic age. There are two types of fermentation based on respiration: Aerobic fermentation and An-aerobic fermentation.

9.2 Aerobic Fermentation

Aerobic fermentation is also known as aerobic glycolysis, it occurs in the presence of oxygen. It is a metabolic process by which cells metabolize sugars via fermentation and occurs through the repression of normal respiratory metabolism (also referred to as the Crabtree effect in yeast). Oxygen limitation is the major problem in aerobic fermentation because oxygen has a low solubility in water. Dissolved oxygen (DO) concentration is generally kept as high as possible by increasing the oxygen transfer rate (OTR). Aerobic fermentation is usually a shorter and more intense process than anaerobic fermentation.

➢ General Process for Aerobic Fermentation

1. **Glucose Breakdown (Glycolysis) :** Glucose ($C_6H_{12}O_6$) is first broken down into pyruvate through glycolysis, a process that takes place in the cytoplasm. This step generates a small amount of energy (2 ATP molecules) and produces NADH, which will be used in later stages of respiration.

2. **Krebs Cycle (Citric Acid Cycle) :** In the presence of oxygen, pyruvate enters the mitochondria (in eukaryotes) and is converted into acetyl-CoA. Acetyl-CoA enters the Krebs cycle, where it undergoes a series of chemical reactions that produce ATP, NADH, and $FADH_2$.
3. **Electron Transport Chain (ETC) :** The NADH and $FADH_2$ produced in the previous steps donate electrons to the electron transport chain located in the mitochondria. This process generates a large amount of ATP and results in the reduction of oxygen to water.

➢ Byproducts

- Water (H_2O)
- Carbon dioxide (CO_2)

Energy Yield : High energy yield—typically 36–38 ATP molecules per glucose molecule.

➢ Example

♦ Yeast in aerobic conditions: When oxygen is available, yeast cells perform aerobic respiration to produce energy, carbon dioxide, and water. This is the process that occurs in the fermentation of beer and wine, but under aerobic conditions, oxygen is used for efficient energy production.

9.3 Anaerobic Fermentation

Anaerobic fermentation is a process in which cells use to extract energy from carbohydrates when oxygen or other electron acceptors are not available in the surrounding environment. This differentiates it from anaerobic respiration, which doesn't use oxygen but does use electron-accepting molecules that come from outside of the cell. Anaerobic fermentation has a broad range of applications. It could be used for the production of various industrial chemicals, such as ethanol, butyl alcohol, acetic acid, lactic acid, hydrogen gas and various nutraceutical molecules with medical benefit.

This process can follow gyclolysis as the next step in the breakdown of glucose and other sugars to produce molecules of adenosine triphosphate (ATP) which create an energy source for the cell. Through this method, a cell is able to regenerate nicotinamide adenine dinuleotide (NAD+) from the reduced form of nicotinamide adenine dinucleotide (NADH). It also relies on enzymes to add a phosphate group to an individual diphosphate (ADP) to produce ATP.

➢ General Process for Anaerobic Fermentation

1. **Glucose Breakdown (Glycolysis) :** Just like in aerobic fermentation, glucose is initially broken down into pyruvate in the cytoplasm, generating 2 ATP molecules and NADH.
2. **Fermentation Pathway :** Since oxygen is not available to fully oxidize the pyruvate into carbon dioxide and water, the pyruvate is converted into different byproducts depending on the type of organism and fermentation process. The key point is that NADH is oxidized back to NAD+ in the process, allowing glycolysis to continue.
   - **Alcoholic fermentation (in yeast and some bacteria) :** Pyruvate is converted into ethanol and carbon dioxide. The process is used by yeast during the production of alcoholic beverages and bread.
   - **Lactic acid fermentation (in muscle cells and certain bacteria) :** Pyruvate is converted into lactic acid. This is the process that occurs in human muscle cells during intense exercise when oxygen is scarce. Lactic acid fermentation also occurs in bacteria used in yogurt production.

➢ Byproducts

- Alcohol (ethanol) in alcoholic fermentation
- Lactic acid in lactic acid fermentation
- Carbon dioxide (CO_2) (especially in alcoholic fermentation)

Energy Yield : Low energy yield—only 2 ATP molecules per glucose molecule, since glycolysis is the only step involved in energy production (no electron transport chain or Krebs cycle).

➢ Examples

- ♦ Yeast (alcoholic fermentation): In the absence of oxygen, yeast converts pyruvate into ethanol and CO_2 during the fermentation of sugars in bread, beer, and wine.
- ♦ Human muscle cells (lactic acid fermentation): During intense exercise, when oxygen is limited, human muscle cells switch to lactic acid fermentation, producing lactic acid as a byproduct.

9.4 Comparison of Aerobic vs Anaerobic Fermentation

Feature	Aerobic Fermentation	Anaerobic Fermentation
Oxygen Requirement	Requires oxygen	Does not require oxygen

Feature	Aerobic Fermentation	Anaerobic Fermentation
End Products	Carbon dioxide (CO_2), water (H_2O)	Ethanol (in alcoholic fermentation) or Lactic acid (in lactic acid fermentation)
Energy Yield	High (36–38 ATP per glucose molecule)	Low (2 ATP per glucose molecule)
Organisms Involved	Most eukaryotic organisms, including humans (in mitochondria)	Yeast, bacteria, and muscle cells under stress
Key Process	Full oxidation of glucose via glycolysis, Krebs cycle, and ETC	Partial breakdown of glucose via glycolysis, followed by fermentation pathways
Examples of Use	Aerobic respiration in human cells, yeast in brewing (when oxygen is present)	Yeast in brewing (when oxygen is absent), muscle cells during exercise, yogurt production

9.5 Production of Ethyl alcohol by Fermentation

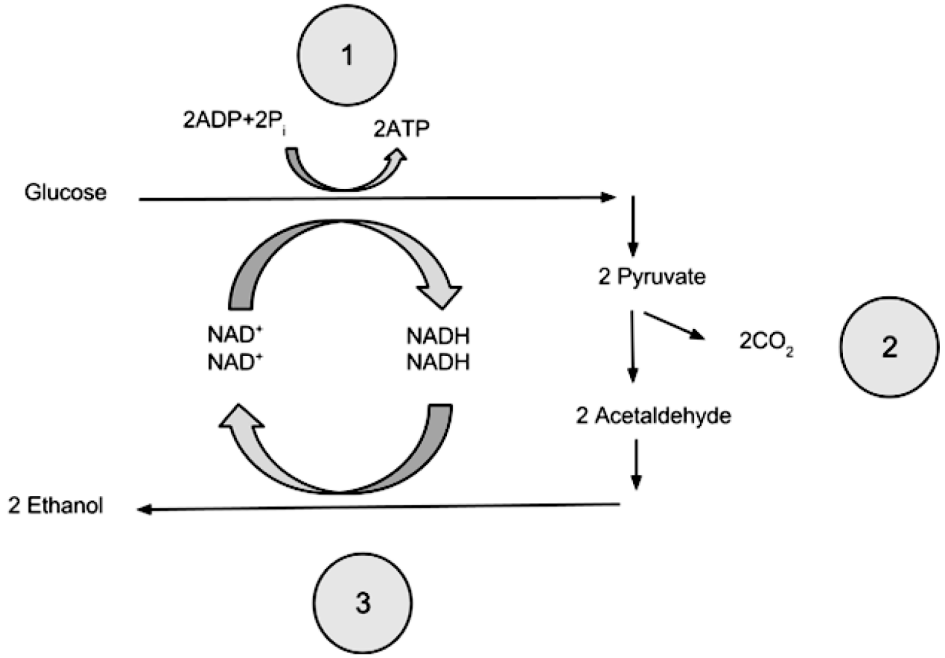
Production of ethyl alcohol by fermentation is also chemically known as Ethanol fermentation. It is a biotechnological process accomplished by yeast in the absence of oxygen, thus alcoholic fermentation is considered as an anaerobic process. In this process sugars such as glucose, sucrose and fructose are converted into cellular energy and thereby produced ethanol and carbon dioxide as metabolic waste product. This conversion can also be performed by some kinds of bacteria or a few other microorganisms. Among the yeasts, *Saccharomyces cerevisiae* is the most commonly used while among the bacteria, *Zymomonasmobilis* is the most frequently employed for ethanol production. Alcoholic fermentation produces beer and wine.

Alcoholic fermentation includes three steps discussed below—

i) Alcoholic fermentation begins with the breakdown of sugars (glucose) by yeasts to form two pyruvate molecules, which is also known as glycolysis. The energy released by this exothermic reactionis used to phosphorylate two ADP molecules, yielding two ATP molecules. Two molecules of NAD+ are also reduced to NADH.

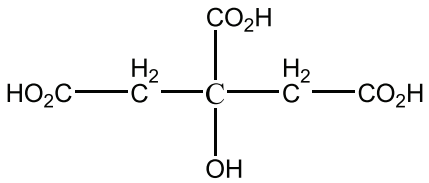
ii) The two pyruvate molecules are broken down, yielding two acetaldehyde molecules and giving off two molecules of carbon dioxide.

iii) The two molecules of NADH reduce the two acetaldehyde molecules to two molecules of ethanol and this converts NAD+ back into NADH. The flowchart is given next page.



9.6 Production of citric acid by Fermentation Process

Citric acid (2-hydroxy-1,2,3-propane tri-carboxylic acid), a natural constituent and common metabolite, is the most important organic acid produced in tonnage and is extensively used in food and pharmaceutical industries.



Chemical structure of citric acid

Citric acid found primarily in several varieties of varieties of fruits and vegetables with citrus fruits such as lemons and limes containing the highest amounts of citric acid. This acid has many uses, including as a food additive / preservative, ingredient in cosmetic products and as a powerful cleaving agent. A large number of micro-organisms including bacteria, fungi and yeasts have been employed to produce citric acid.

For the production of citric acid, fermentation is the most economical and widely used way. The industrial citric acid production can be carried out in three different ways—

i) **Surface Fermentation :** Surface fermentation using *Aspergillus niger* may be done on rice bran as is the case in Japan, or in liquid solution in flat aluminium pans. Special strains of *Aspergillus niger* which can produce citric acid despite the high content of trace metals in rice bran are used. The citric acid is extracted from the bran by leaching and is then precipitated from the resulting solution as calcium citrate.

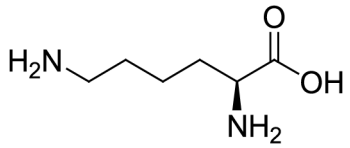
ii) **Solid state Fermentation :** It is also known as Koji process and it is the simplest method for the production of citric acid.

iii) **Submerged Fermentation :** Citric acid produced mainly by submerged fermentation using *Aspergillus niger* from different sources of carbohydrates, such as molasses and starch-based media. In this case, the strains are inoculated of about 15cm depth in fermentation tank. The culture is enhanced by giving aeration using air bubbles and it is allowed to grow for about 5-14 days at 27-30 degree Celsius. The citric acid is produced in the fermentation tank and it is purified.

Each of these methods has its advantages, but submerged fermentation is the most widely used in industry due to its efficiency and scalability.

9.7 Production of Lysine by Fermentation Process

Lysine is an essential, economically important amino acid. Since it is need for bone formation so children and growing animals have a high requirement of lysine. It is used medically as a nutrient in form of supplements and medicines. Lysine also has some pharmaceutical applications in the formulation of diets with balanced amino acid composition and in amino acid infusions. Lysine is present in two forms, L-form and D-form. L-lysine is biologically active.



L-lysine

Two major biotechnological processes are used to manufacture lysine, one is the enzymatic conversion of dl-α-amino-ε-caprolactam and the other one is fermentation. L-lysine is mainly produced by fermentation using strains of corynebacteria, especially *Corynebacterium glutamicum*. The process can be divided into three main parts—fermentation; product recovery; product concentration, drying and packaging. The optimum fermentation temperature is 35-37°C and the optimum pH is 7.2.

9.7.1 Summary of Lysine Fermentation Process

i) **Preparation of Culture Media :** Process water, glucose, and nutrients are mixed to prepare the media for both batch and fed-batch phases.

ii) **Fermentation Step (Fed-Batch Mode, Aerobic Conditions) :**

a) **Batch Phase :** The microorganism seed is inoculated into fermenters containing batch media.

b) **Transition to Fed-Batch :** Once glucose is exhausted, the fed-batch phase begins.

c) **Fed-Batch Phase :** Continuous addition of glucose and nutrients until the desired L-lysine concentration is achieved.

d) The final fermentation broth is sent to a buffer tank for steady down-stream processing.

iii) **Product Recovery & Purification :**

- **Ultra-Filtration :** Removes cell debris and suspended solids.
- **Ion-Exchange Columns :** Selective adsorption of L-lysine.
- **Elution :** L-lysine is washed out using aqueous ammonia solution.
- **Concentration :** The eluted lysine is mixed with mother liquor and concentrated via evaporation.

iv) **Conversion to L-Lysine HCl :** Hydrochloric acid is added to free L-lysine, converting it into L-lysine HCl. The solution is crystallized, and the solid L-lysine HCl is filtered and collected.

This process ensures high purity and yield of L-lysine, widely used in animal feed, food supplements, and pharmaceuticals.

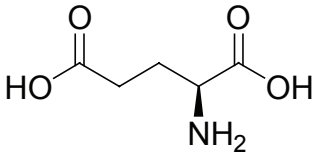
9.8 Production of L-Glutamic Acid by Fermentation

L-glutamic acid is a key amino acid involved in protein biosynthesis and is widely found in various foods. It is primarily used as a food additive and flavor enhancer in the form of its sodium salt, monosodium glutamate (MSG). Additionally, glutamic acid plays a crucial role in brain metabolism, and its analogs are used in the treatment of neuropathic disorders.

9.8.1 Biotechnological Production vs. Chemical Synthesis

Chemical synthesis of L-glutamic acid is not preferred due to the formation of a racemic mixture (containing both D and L-isomers), which reduces purity and

efficiency. Instead, microbial fermentation using *Corynebacterium glutamicum* in a submerged fermentation process is widely employed for large-scale production.



L-glutamic acid

9.8.2 Fermentation Process

i) **Preparation of Culture Medium :** The fermentation medium contains a carbon source (glucose) and a nitrogen source (urea). The medium is sterilized with steam in the fermenter to prevent contamination.

ii) **Fermentation Conditions :** Once cooled to 30°C, the fermenter is inoculated with *Corynebacterium glutamicum* in an appropriate concentration. The fermentation lasts for 36-48 hours, with the following controlled conditions—

- **pH :** Maintained between 7.0 – 7.8
- **Temperature :** 30-35°C
- **Aeration :** Carefully regulated to support microbial growth and glutamic acid production.

iii) **Product Isolation and Purification :**

- **Cell Separation :** The fermentation broth is filtered to remove microbial cells.
- **Crude Isolation :** The broth is acidified to precipitate L-glutamic acid.
- **Purification :** The precipitated L-glutamic acid is crystallized, filtered, dried, and packaged for various applications.

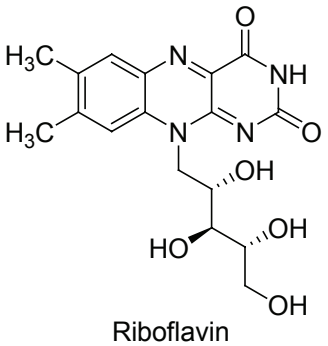
The submerged fermentation method is the most efficient approach for producing high-purity L-glutamic acid, making it the preferred method in the biotechnology industry.

9.8.3 Applications of L-Glutamic Acid

- Food Industry: Used as a flavor enhancer in the form of MSG.
- Pharmaceuticals: Utilized in the treatment of neurological disorders.
- Biochemical Research: Plays a role in metabolic and neurological studies.

9.9 Production of Vitamin B_2 (Riboflavin) by Fermentation

Riboflavin (Vitamin B_2) is a water-soluble vitamin essential for growth, reproduction, and overall metabolism in humans and animals. It serves as a precursor for the enzymes Flavin Adenine Dinucleotide (FAD) and Flavin Mononucleotide (FMN), which play a crucial role in redox reactions involved in the metabolism of carbohydrates, lipids, ketone bodies, and proteins, enabling organisms to derive energy.



Riboflavin

9.9.1 Industrial Production of Riboflavin

Riboflavin is naturally produced by plants and many microorganisms. It can be synthesized through chemical methods or microbial fermentation. However, the fermentation process is more cost-effective as it allows for single-step production, unlike the multi-stage and expensive chemical synthesis. Due to its economic and environmental benefits, major producers such as BASF, Roche, ADM/Aventis, and Hubei Guangji prefer fermentation-based production.

9.9.2 Summary of the Fermentation Process

i) **Microorganisms Used :** Although some bacteria (Clostridium species) and yeasts (Candida species) produce riboflavin, the best producers are the *Ascomycete fungi:*
   - *Eremothecium ashbyii*
   - *Ashbya gossypii*

ii) **Seed Culture Preparation :**
   - The fermentation process starts with seed culture preparation, which is carried out in multiple seed fermenters over several steps.
   - The final seed culture serves as the inoculum for the main fermentation.

iii) **Fermentation Process :** The necessary seed cultures are prepared in dif-

ferent seed fermenters in several steps. The last seed culture is the start inoculum for the main fermentation. The duration of a seed-fermentation is around 50 hours, while the main fermentation lasts about 500 hours. During this time the strain produces 27 g/L riboflavin. Fermentation requires aeration accomplished by a gas compressor and a sterile filter and exhaust gases are filtered by a second filter. A portion of the harvested broth is transferred to another tank and used as an inoculum for the next batch to maintain production continuity.

iv) Product Recovery and Purification :

- After fermentation, the broth is collected in a harvest tank.
- The riboflavin is crystallized by evaporating excess water.
- The final powdered product is obtained through drying.

The fermentation-based production of riboflavin is preferred due to its high efficiency, lower production costs, and eco-friendly nature, making it the dominant method in the industry.

9.9.3 Applications of Riboflavin

- Food and Beverages: Used as a vitamin supplement and food coloring.
- Pharmaceutical Industry: Essential for treating riboflavin deficiencies.
- Animal Feed: Used as a nutritional additive to enhance livestock health.

9.10 Production of Vitamin B_{12} (Cyanocobalamin) by Fermentation

Vitamin B_{12}, also known as Cyanocobalamin, belongs to the Cobalamin family of compounds. It is a water-soluble vitamin essential for the normal functioning of the brain and nervous system and the formation of red blood cells. It plays a crucial role in DNA synthesis, fatty acid metabolism, and amino acid metabolism in every cell of the human body. Due to its importance, Vitamin B_{12} is widely used in the medical and food industries. A deficiency in Vitamin B_{12} can lead to pernicious anemia and other health complications.

9.10.1 Industrial Production of Vitamin B_{12}

Unlike other vitamins, Vitamin B_{12} is exclusively synthesized by microorganisms and cannot be produced by plants or animals. It is the largest and most structurally complex vitamin and is industrially manufactured through bacterial fermentation.

The submerged culture fermentation process is commonly used, completing production within 3-4 days.

9.10.2 Summary of Fermentation Process:

i) **Microorganisms Used :** The following microorganisms are employed for industrial B_{12} production—
   - **Bacteria :** *Pseudomonas denitrificans, Propionibacterium shermanii, Propionibacterium freudenreichii, Bacillus megaterium, Bacillus coagulans*
   - **Actinomycetes :** *Streptomyces griseus, Streptomyces olivaceus*

ii) **Steps involved in the Fermentation Process :**
   a) **Formulation of the Medium :** A nutrient-rich medium is prepared using glucose as the primary carbon source.
   b) **Sterilization of the Medium :** The medium is sterilized to eliminate contamination.
   c) **Starter Culture Preparation :** A small culture of selected microorganisms is grown and used as an inoculum.
   d) **Anaerobic Fermentation :** The fermentation begins under anaerobic conditions, allowing initial microbial growth.
   e) **Aerobic Fermentation :** The process shifts to aerobic conditions, stimulating Vitamin B_{12} synthesis.
   f) **Recovery and Purification :** The Vitamin B_{12} is extracted, purified, and converted into Cyanocobalamin for medical and food applications.

The bacterial fermentation method is the most effective and widely used technique for Vitamin B_{12} production, ensuring high yields and purity while maintaining cost efficiency.

yields and purity

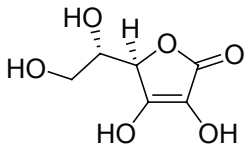
9.10.3 Applications of Vitamin B_{12}

- Medical Industry: Used in treating Vitamin B_{12} deficiency, anemia, and neurological disorders.
- Food Industry: Added as a dietary supplement in fortified foods.
- Animal Feed: Used as a nutritional supplement for livestock and poultry.

9.11 Production of Vitamin C (Ascorbic Acid) by Fermentation

Vitamin C, also known as Ascorbic Acid or Ascorbate, is an essential nutrient for humans and a few other mammals. It plays a vital role in enzyme function, immune

system support, and serves as a powerful antioxidant. Due to its importance, Vitamin C is widely used in the food, beverage, animal feed, and pharmaceutical industries.



Vitamin C

9.11.1 Methods of Vitamin C Production

Commercial production of Vitamin C has been achieved through various methods, including—

- Extraction from plants
- Chemical synthesis
- Fermentation-based processes
- Mixed fermentation methods
- Currently, two main processes are used for industrial production—
  1. Reichstein Process (Traditional Method)
  2. Two-Stage Fermentation Process (Modern Method)

However, the Reichstein Process is considered less eco-friendly due to the following reasons—

- Use of explosive hydrogen gas (H_2)
- Requirement of high pressure and temperature
- Use of toxic chemicals like acetone and potassium permanganate ($KMnO_4$), which are harmful to the environment

As a result, the two-stage fermentation process is now widely preferred.

9.11.2 Two-Stage Fermentation Process

In this modern method, a second fermentation step replaces the chemical reactions used in the Reichstein process to produce 2-Keto-L-Gulonic Acid (2-KLG), a key intermediate in Vitamin C synthesis.

❖ **Step 1 :** Conversion of D-Sorbitol to L-Sorbose: D-Sorbitol (derived from glucose) undergoes fermentation using *Gluconobacter oxydans*. This results in the formation of L-Sorbose, a key intermediate.

❖ **Step 2 :** Conversion of L-Sorbose to 2-Keto-L-Gulonic Acid (2-KLG): In a mixed fermentation, *Ketogulonicigenium vulgare* and *Bacillus spp*. convert

L-Sorbose into 2-KLG. This step replaces the chemical oxidation step in the Reichstein process.

❖ **Final Step :** Chemical Conversion of 2-KLG to Vitamin C: 2-KLG is chemically converted into Ascorbic Acid (Vitamin C) through esterification and cyclization.

9.11.3 Advantages of the Two-Stage Fermentation Process

- **Eco-Friendly :** Eliminates toxic chemicals like acetone and potassium permanganate ($KMnO_4$)
- **Energy Efficient :** Operates at lower temperatures and pressures compared to the Reichstein process
- **Widely Used :** Adopted globally, especially in China, where it dominates Vitamin C production

9.12 Summary

- Aerobic Fermentation requires oxygen and typically yields high ATP production. It involves glycolysis, the Krebs cycle, and the electron transport chain, leading to byproducts such as carbon dioxide and water.
- Anaerobic Fermentation occurs without oxygen and produces less ATP. Common types include lactic acid fermentation and alcoholic fermentation, with products such as ethanol, lactic acid, and carbon dioxide.
- Ethanol is produced via alcoholic fermentation by *Saccharomyces cerevisiae* in anaerobic conditions, primarily for biofuel and alcoholic beverages.
- Citric Acid is produced using *Aspergillus niger* in submerged fermentation, widely used in food and pharmaceuticals.
- Lysine (an essential amino acid) is produced using *Corynebacterium glutamicum*, crucial for animal feed.
- Glutamic Acid is produced by *Corynebacterium glutamicum*, used in food industries as monosodium glutamate (MSG).
- Vitamin B_2 (Riboflavin) is synthesized using Ashbya gossypii or Bacillus subtilis, essential for metabolism.
- Vitamin B_{12} (Cobalamin) is industrially produced using *Pseudomonas denitrificans* and *Propionibacterium shermanii*, critical for red blood cell formation.
- Vitamin C (Ascorbic Acid) is synthesized using microbial fermentation combined with chemical synthesis, widely used as an antioxidant.

9.13 Exercises

A. Multiple-Choice Questions on Aerobic and Anaerobic Fermentation

1. What is another name for aerobic fermentation?
   a) Anaerobic glycolysis
   b) Aerobic glycolysis
   c) Krebs cycle
   d) Alcoholic fermentation

Answer : b) Aerobic glycolysis

2. Which of the following is a major challenge in aerobic fermentation?
   a) Lack of glucose
   b) Oxygen limitation
   c) High carbon dioxide levels
   d) Low ATP production

Answer : b) Oxygen limitation

3. What is the typical energy yield of aerobic fermentation per glucose molecule?
   a) 2 ATP
   b) 10 ATP
   c) 36–38 ATP
   d) 100 ATP

Answer : c) 36–38 ATP

4. Which of the following processes occurs in the mitochondria during aerobic fermentation?
   a) Glycolysis
   b) Fermentation pathway
   c) Krebs cycle
   d) None of the above

Answer : c) Krebs cycle

5. What are the end products of aerobic fermentation?
   a) Lactic acid and ATP
   b) Ethanol and carbon dioxide

c) Water and carbon dioxide

d) Acetic acid and ATP

Answer : c) Water and carbon dioxide

6. What is the main purpose of the electron transport chain (ETC) in aerobic respiration?

a) Break down glucose into pyruvate

b) Convert ATP into ADP

c) Generate ATP and reduce oxygen to water

d) Produce ethanol and carbon dioxide

Answer : c) Generate ATP and reduce oxygen to water

7. In yeast, which condition promotes aerobic fermentation?

a) Absence of oxygen

b) Presence of oxygen

c) High ethanol concentration

d) Low sugar levels

Answer : b) Presence of oxygen

8. What is the main difference between anaerobic fermentation and anaerobic respiration?

a) Anaerobic respiration requires oxygen

b) Anaerobic fermentation does not use an external electron acceptor

c) Anaerobic fermentation produces more ATP than aerobic respiration

d) Anaerobic respiration does not involve glycolysis

Answer : b) Anaerobic fermentation does not use an external electron acceptor

9. What are the byproducts of lactic acid fermentation?

a) Ethanol and carbon dioxide

b) Lactic acid and ATP

c) Water and oxygen

d) Glucose and pyruvate

Answer : b) Lactic acid and ATP

10. Which of the following microorganisms is commonly used for the industrial production of citric acid?

a) Saccharomyces cerevisiae

b) Zymomonas mobilis

c) Aspergillus niger

d) Corynebacterium glutamicum

Answer : *c) Aspergillus niger*

11. What is the preferred method for large-scale production of citric acid?
    a) Solid-state fermentation
    b) Submerged fermentation
    c) Surface fermentation
    d) Chemical synthesis

Answer : b) Submerged fermentation

12. What is the most common microorganism used in ethanol fermentation?
    a) Escherichia coli
    b) Corynebacterium glutamicum
    c) Saccharomyces cerevisiae
    d) Bacillus subtilis

Answer : *c) Saccharomyces cerevisiae*

13. What is the main function of L-glutamic acid in the food industry?
    a) Vitamin supplement
    b) Food coloring
    c) Flavor enhancer (MSG)
    d) Preservative

Answer: c) Flavor enhancer (MSG)

14. Which vitamin is industrially produced using *Pseudomonas denitrificans* and *Propionibacterium shermanii*?
    a) Vitamin B_1
    b) Vitamin B_2
    c) Vitamin B_{12}
    d) Vitamin C

Answer : c) Vitamin B_{12}

15. Which process is used to convert glucose into ethanol and carbon dioxide in the absence of oxygen?
    a) Lactic acid fermentation
    b) Alcoholic fermentation
    c) Krebs cycle
    d) Glycolysis

Answer : b) Alcoholic fermentation

B. Short Answer

1. What is aerobic fermentation, and why is it also called aerobic glycolysis?
2. Why is oxygen limitation a major problem in aerobic fermentation?
3. What are the three main steps of aerobic fermentation?
4. What is the role of the Krebs cycle in aerobic fermentation?
5. What are the byproducts of aerobic fermentation?
6. Give an example of aerobic fermentation in yeast.
7. What differentiates anaerobic fermentation from anaerobic respiration?
8. Name some industrial products obtained through anaerobic fermentation.
9. What are the two main types of anaerobic fermentation pathways?
10. What are the byproducts of alcoholic fermentation?
11. What are the key differences between aerobic and anaerobic fermentation in terms of oxygen requirement?
12. Why is aerobic fermentation considered more efficient than anaerobic fermentation?
13. What microorganisms are commonly used for ethanol fermentation?
14. What are the three main steps involved in ethanol fermentation?
15. Which microorganism is primarily used for citric acid production?
16. Why is submerged fermentation the most preferred method in industry?
17. What microorganism is primarily used for lysine fermentation?
18. What are the major steps in lysine fermentation?
19. What are the key fermentation conditions for L-glutamic acid production?
20. Why is riboflavin (Vitamin B_2) essential for human health?
21. What are the major steps involved in riboflavin fermentation?
22. What are the key microorganisms used for Vitamin B_{12} production?
23. Describe the steps involved in Vitamin B_{12} fermentation.

Unit 10 : Production of Antibiotics by fermentation process

10.0 Objectives

By the end of this chapter, learners should be able to—

- Recognize the specific microorganisms responsible for the natural production of each antibiotic:
- Understand the fermentation techniques employed in the industrial-scale production of the antibiotics, including Penicillin, Cephalosporin, Chloromycetin and Streptomycin,
- Analyze the metabolic pathways and genetic mechanisms that lead to the synthesis of these antibiotics within their respective microorganisms.
- Examine the scale-up processes, including strain improvement, fed-batch cultivation, and downstream processing, that facilitate the mass production of these antibiotics for clinical use.

10.1 Introduction

The advent of antibiotics stands as a cornerstone in medical history, revolutionizing the treatment of bacterial infections and saving countless lives. Central to this achievement is the large-scale production of antibiotics through fermentation processes, a feat that has enabled widespread accessibility and therapeutic application.

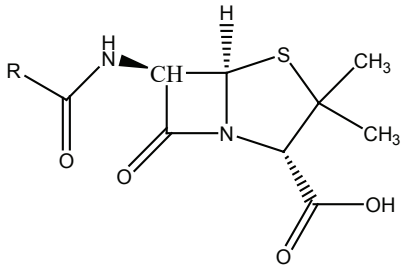
Fermentation, a metabolic process harnessed by microorganisms, has been instrumental in the biosynthesis of various antibiotics. This chapter delves into the production methodologies of four pivotal antibiotics: Penicillin, Cephalosporin, Chloramphenicol, and Streptomycin.

10.2 Antibiotics

An antibiotic is a type of antimicrobial substance active against bacteria. It is the most important type of antibacterial agent for fighting bacterial infections, and antibiotic medications are widely used in the treatment and prevention of such infections. They may either kill or inhibit the growth of bacteria. Here we will discuss about the production process of few antibiotics using fermentation process.

10.3 Production of Penicillin by Fermentation

Penicillin is the oldest and one of the most commonly used groups of antibiotics at present. They are derived from the mold/fungi Penicillium and it is also known as *Penicillium notatum*. It can be found on salted food products, but it is mostly found in indoor environments, especially in damp or water-damaged buildings. It is common in temperature and subtropical. Penicillin is the source of several β-lactum antibiotics, which inhibits biosynthesis of bacterial cell wall.



Penicillin

Penicillin can be divided into two groups, namely natural and semisynthetic penicillins. Semisynthetic penicillins are prepared from (+)-6-aminopenicillanic acid, on the other hand, natural Penicillins are produced from the fermentation of the fungus *Penicillium chrysogenum*. Penicillin production is previously achieved by surface process i.e. Solid state fermentation and surface liquid fermentation. Nowadays, a commercial production is carried out by fed batch process mentioned below.

➢ Inoculum (microbial culture) Preparation

Penicillium chrysogenum is the most widely used high-yielding strain for penicillin production. The primary objective of inoculum preparation is to develop a

pure and sufficient microbial culture for fermentation. This process involves several sequential steps—

i) **Starter Culture Preparation :** A pure starter culture is required for inoculation.

   Growth on Solid Media—The culture is initially grown on solid media, followed by one or two growth stages in shaken flask cultures to create a cell suspension.

ii) **Seed Tank Transfer :** The prepared suspension is then transferred to seed tanks for further growth and biomass development.

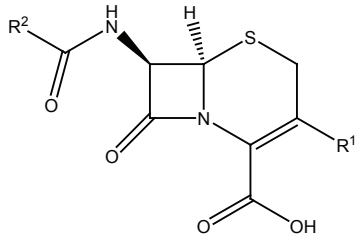
iii) **Primary Fermentation Transfer :** After 24-28 hours, the seed tank culture is transferred to the primary fermentation tanks to initiate large-scale production.

iv) **Controlled Fermentation Conditions :** Essential bioprocess parameters such as temperature, pH, aeration, and agitation must be carefully regulated to ensure optimal microbial growth and product yield.

Additionally, factors such as corn syrup supplementation, strain selection, mutation and selection techniques, and sexual reproduction play a crucial role in enhancing penicillin yield.

10.4 Production of Cephalosporin by Fermentation

Cephalosporins are the second major group of β-lactum, derived from the micro-organism *Acrimonium chrysogenum.* These are closely related to the Penicillins in both the structure and mode of action and are used to treat bacterial infections.



Core structure of cephalosporins

Cephalosporin is a popular antibiotic because of its excellent characteristics such as broad spectrum of activity, low toxicity, high safety profile, oral and parenteral preparations, and resistance to β-lactamase than Penicillin.

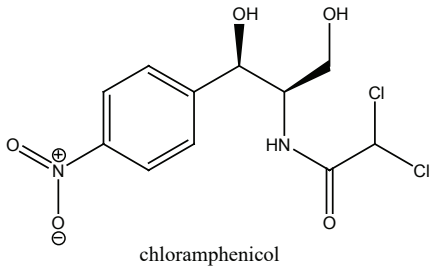
➢ Fermentation Process

Cephalosporin C is easily produced from the fungus *Acremonium chrysogenum* by the process of fermentation in a bioreactor under optimum reaction conditions to

obtain maximum yield of the antibiotic. The fermentation process concerned with the production of cephalosporin is similar to that of penicillin. The culture media consists of corn steep liquor and soy flour-based media in a continuous feeding system. The other ingredients of the medium includesucrose, glucose and ammonium salts. Methionine is added as a source of sulfur. The fermentation is carried out at temperature 25-28°C and at pH 6-7. The growth of micro-organisms substantially increases with good oxygen supply, although during production phase, oxygen consumption declines. Cephalosporin C from the culture broth can be recovered by ion-exchange resins and by using column chromatography. Cephalosporin C can be precipitated as zinc, sodium or potassium salt and isolated.

10.5 Production of Chloromycetin (Chloramphenicol) by Fermentation

Chloramphenicol is an antibiotic produced by *Streptomycetes venezuelae* in 1947. It is useful for the treatment of a number of bacterial infections.



chloramphenicol

Chloramphenicol is a broad spectrum antibiotic that typically stops bacterial growth by stopping the production of proteins. It can act on both Gram-positive and Gram-negative, actinomycetes, rickettsiae and chlamydias. Because of its toxic effect on bone marrow, Chloramphenicol has not been widely used but its toxicity can be reduced if therapy is conducted carefully. Chloramphenicol can be produced by fermentation:

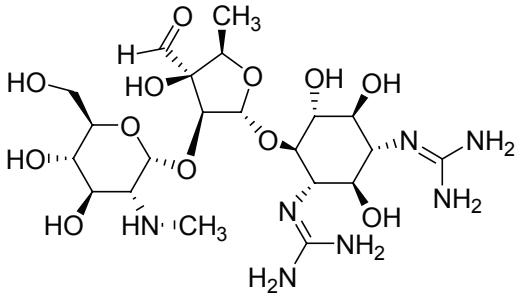
➢ Fermentation Process

The fermentation is carried out in 30 liters Fermenter containing 18-liter medium consisting of glycerol (1%), yeast extract, sodium chloride (0.5%) and pH is adjusted to 7.5. The fermentation is carried out at 25°C for 3-4 days. Chloramphenicol is extracted from the clarified broth. The filtrate is extracted either with ethyl or diluted with kerosene and then washed with dilute acetic acid, sodium carbonate and water. The lipids are removed by petroleum ether and the crude product is decolorized by passing the organic solution through a column of char-

coal or alumina. The purified product is recrystallized from ethylene or ether and petroleum ether mixture.

10.6 Production of Streptomycin by Fermentation

Streptomycin is an antibiotic, produced by *Streptomyces griseus.* It is used to treat a number of bacterial infections, this includes tuberculosis, endocarditis, plague, tularemia, *Mycobacterium avium* complex, brucellosis, *Burkholderia* infection and rat bite fever.



Streptomycin

It is particularly active against Gram-negative bacteria and against tuberculosis organism, *Mycobacterium tuberculosis*. However, it proved to be useful in the treatment of infections caused by Gram-positive especially resistant to penicillin. It is also useful in the control of plant diseases caused by bacteria as it acts systemically in plants.

➢ Fermentation Process

Spores of *S. griseus* are inoculated into medium to establish a culture with high mycelia biomass for introduction into inoculums tank, using inoculums to initiate the fermentation process. Yield in this production vessel responds to high aeration and agitation condition. The optimum fermentation temperature is in the range of 25-30°C and the optimum pH range in between 7-8. High rate to streptomycin production, however, occurs in the pH range of 7.6-8. The process of fermentation is highly aerobic and lasts approximately for 5 to 7 days and passes through 3 phases—

- The first phase (it takes about 24-28 hours)
- The second phase (it lasts for 2 days)
- The third phase (harvested before celllysis)

After completion of fermentation the mycelium is separated from the broth by filtration and streptomycin is recovered then the fermentation broth is acidified,

filtered and neutralized. It is then passed through a column containing a cation exchange resin so that streptomycin is adsorbed from the broth. The column is then washed. The streptomycin is dissolved in methanol and filtered. Then acetone is added to the filtrate to precipitate the antibiotic. The precipitate is again washed with acetone and vacuum dried and purified further by dissolving in methanol. The pure form of streptomycin is extracted as calcium chloride complex.

10.7 Summary

- Antibiotics are vital antimicrobial agents that combat bacterial infections by either killing bacteria or inhibiting their growth.
- Penicillin, one of the earliest discovered antibiotics, is produced through the fermentation of the fungus *Penicillium chrysogenum*.
- Cephalosporins, closely related to penicillins, are synthesized by the fungus *Acremonium chrysogenum* (formerly known as *Cephalosporium acremonium*).
- Chloramphenicol, a broad-spectrum antibiotic, is produced by the bacterium *Streptomyces venezuelae*.
- Streptomycin, effective against a variety of bacterial infections including tuberculosis, is produced by the bacterium *Streptomyces griseus*.

10.8 Exercises

A. Answer the following questions (MCQ)

1. Which microorganism is primarily used for the commercial production of penicillin?
   a) *Streptomyces griseus*
   b) *Acremonium chrysogenum*
   c) *Penicillium chrysogenum*
   d) *Streptomyces venezuelae*

Answer : c) *Penicillium chrysogenum*

2. Cephalosporin C is produced by which microorganism?
   a) *Penicillium notatum*
   b) *Acremonium chrysogenum*
   c) *Streptomyces griseus*
   d) *Streptomyces venezuelae*

Answer : b) *Acremonium chrysogenum*

3. Which antibiotic is known for its broad-spectrum activity but has limited use due to its toxic effect on bone marrow?
   a) Penicillin
   b) Cephalosporin
   c) Chloramphenicol
   d) Streptomycin

Answer : c) Chloramphenicol

4. Streptomycin is particularly active against which type of bacteria?
   a) Gram-positive bacteria
   b) Gram-negative bacteria
   c) Both Gram-positive and Gram-negative bacteria
   d) Neither Gram-positive nor Gram-negative bacteria

Answer : b) Gram-negative bacteria

5. Which of the following antibiotics is produced by *Streptomyces venezuelae*?
   a) Penicillin
   b) Cephalosporin
   c) Chloramphenicol
   d) Streptomycin

Answer : c) Chloramphenicol

6. The fermentation process for penicillin production has evolved from surface processes to which modern method?
   a) Solid-state fermentation
   b) Surface liquid fermentation
   c) Fed-batch process
   d) Continuous fermentation

Answer : c) Fed-batch process

7. Which of the following is NOT a characteristic of cephalosporin?
   a) Broad spectrum of activity
   b) High toxicity
   c) Resistance to β-lactamase
   d) Available in oral and parenteral forms

Answer : b) High toxicity

8. During the fermentation process for chloramphenicol production, which medium component serves as the primary carbon source?
   a) Yeast extract
   b) Sodium chloride
   c) Glycerol
   d) Methionine

Answer : c) Glycerol

9. What is the optimal temperature range for the fermentation process in streptomycin production?
   a) 20-25°C
   b) 25-30°C
   c) 30-35°C
   d) 35-40°C

Answer : b) 25-30°C

10. Which phase of streptomycin fermentation lasts approximately 24-28 hours?
    a) First phase
    b) Second phase
    c) Third phase
    d) Harvesting phase

Answer : a) First phase

B. Answer the following questions **(1 Mark for Each)**

i) How many types of fermentation present based on respiration?

ii) What are the optimum fermentation conditions for the production of Lysine?

C. Answer the following questions **(2 Marks for Each)**

i) What is fermentation?

ii) Write down the use of fermentation?

iii) What is the main difference between aerobic and anaerobic fermentation?

iv) Write down the name of yeast and bacteria, which are commonly used in ethanol fermentation?

v) Explain submerged fermentation for the production of Citric acid.

vi) Which type of fermentation is most effective, aerobic or anaerobic? Explain your answer.

vii) What are the media used for the production of Chloramphenicol in fermentation?

viii) What is the advantage of Vitamin B_{12} – fermentation process over chemical process?

ix) Write down some riboflavin producers in fermentation.

x) What is the key role of Vitamin B_{12} in human body?

D. Answer the following questions (4 Marks for Each)

i) Classified Cephalosporin according to generation.

ii) How Streptomycin is recovered after fermentation?

iii) What are the disadvantages of Reichstein Process for the production of Vitamin C? How it is overcome in two-stage fermentation process?

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