PHARMACEUTICAL PRODUCTION TECHNIQUES

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PROJECT ASSIGNMENT

- Describe the development of a drug product in three stages
  - Choice of a drug formulation
  - Description of the disease, the drug substance and the drug product
  - Description of the production process and of critical points for validation
- Starting point: description in article of an active substance
- Groups of 4-5 persons
What is the role of pharmaceutical discipline?

Behind a dosage form such as a tablet there is a plenty of information and science.

The major pharmaceutical subjects:

- Pharmaceutical chemistry
- Pharmacognosy
- Pharmaceutical technology
- Biopharmacy
- Pharmacology
- Pharmaceutical management

What is pharmaceutics?

Originally, the pharmaceutics (farmacia) is the field which deals with the medications, their preparation and dispensing. This is the science and the art of preparation and dispensing of medicines.
Main specific subjects:
Pharmaceutical chemistry

• **Deals with:**
  – Chemical structure of ingredients
    • Synthetization of APIs
    • Structure - effect correlation
    • Biological effect
  – Qualitative and quantitative analysis
    (according to Ph. Eur)
  – Identification of substances
    • Impurities
    • Content determination (assays)
  – Procedures and methods of examination
    • Such as: chromatography, spectroscopy, HPLC, NMR
Main specific subjects:
Pharmaceutical technology

• Deals with:
  – Magistral preparation
  – Industrial manufacture
  – Formulation of medicines, preparations
  – Dosage forms (based on Ph. Eur.)
  – Examination of dosage forms
  – Operations and procedures of manufacturing medicines
  – Drug delivery design
Papyrus Ebers has been found in Luxor in 1862 and written in 1600 B.C. contains 877 prescriptions, medical advices and prayers.

Georg Ebers
German Egyptologist

Hippocrates was born on the Greek Island of Cos in 460 B.C. derived himself from Asclepius and tried to find the causes of diseases and the operation of the body. The religious healing was developed to scientific medicine in Asclepius by him.

Medications made of plants and special diets were used for healing. (Surgery without pain relief)
Medical doctor and pharmacist, the most famous one of the ancient Greek-roman school.

Only 80 of his more than hundreds books remained, which are anatomical, physiological, internal medicine and pharmacological books.

Claudius Galenus (A.D. 129-199)

He introduced drug mixtures and galenicals.

He wrote the production method of certain preparations and the necessary tools.
PRESENT
OSMOTIC RELEASE ORAL TABLET
HALVING OF TABLETS

Drug layer (blue) is pre-divided into exact 1/2 doses

Drug-free break layer (white)

DRUG LAYER
1/2 dose is exact

Tablet breaks through drug-free layer
3D PRINTING TECHNOLOGY IN THE PHARMACEUTICALS
Targeted Drug Therapy

Active/passive targeting

Tumor cell

Target cell

nucleus

2. step

Targeting agent

1. step
Entry of Biotechnology - 1978
Introduction to the pharmaceutical terminology
Introduction to the pharmaceutical technology
WHAT IS PHARMACEUTICAL?

- **Pharmaceutical** is a drug or finished form of a drug used to treat, cure, diagnose or prevent of a disease or to alter the physiological body functions for well being.

- A **pharmaceutical drug** (also referred to as medicine, medication, or simply as drug) is a drug used to diagnose, cure, treat, or prevent disease.

- **Pharmaceutical products** – more commonly known as medicines or drugs – are a fundamental component of both modern and traditional medicine.

- It is essential that such products are safe, effective, and of good quality, and are prescribed and used rationally.
DRUGS ARE CLASSIFIED IN VARIOUS WAYS

- One of the key divisions is by level of control, which distinguishes prescription drugs (those that a pharmacist dispenses only on the order of a physician, physician assistant, or qualified nurse) from over-the-counter drugs (those that consumers can order for themselves).

- Another key distinction is between traditional small-molecule drugs, usually derived from chemical synthesis, and biopharmaceuticals, which include recombinant proteins, vaccines, blood products used therapeutically (such as IVIG), gene therapy, monoclonal antibodies and cell therapy (for instance, stem-cell therapies).

- Other ways to classify medicines are by mode of action, route of administration, biological system affected, or therapeutic effects.
In Europe, the term is "medicinal product", and it is defined by EU law as: "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."
In the US, a "drug" is:

I. A substance recognized by an official pharmacopoeia or formulary.

II. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

III. A substance (other than food) intended to affect the structure or any function of the body.

IV. A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.

V. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).
CLASSIFICATION-I

*pharmaceutical or a drug is classified on the basis of their origin.*

1) **Drug from natural origin:** Herbal or plant or mineral origin, some drug substances are of marine origin.

2) **Drug from chemical as well as natural origin:** Derived from partial herbal and partial chemical synthesis Chemical, example steroidal drugs.

3) **Drug derived from chemical synthesis.**

4) **Drug derived from animal origin:** For example, hormones, and enzymes.

5) **Drug derived from microbial origin:** Antibiotics

6) **Drug derived by biotechnology genetic-engineering, hybridoma technique for example**

7) **Drug derived from radioactive substances.**
CLASSIFICATION-II

on the basis of pharmacological properties

1) Antipyretics: reducing fever (pyrexia/pyresis)
2) Analgesics: reducing pain (painkillers)
3) Antimalarial drugs: treating malaria
4) Antibiotics: inhibiting germ growth
5) Antiseptics: prevention of germ growth near burns, cuts and wounds
6) Mood stabilizers: lithium and valpromeide
7) Hormone replacements: Premarin
8) Oral contraceptives: Enovid, "biphasic" pill, and "triphasic" pill
9) Stimulants: methylphenidate, amphetamine
10) Tranquilizers: meprobamate, chlorpromazine, reserpine, chlordiazepoxide, diazepam, and alprazolam
11) Statins: lovastatin, pravastatin, and simvastatin
Pharmaceuticals may also be described as "specialty", independent of other classifications, which is an ill defined class of drugs that might be difficult to administer, require special handling during administration, require patient monitoring during and immediately after administration, have particular regulatory requirements restricting their use, and are generally expensive relative to other drugs.
The *pharmaceutical industry* discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications.

They are subject to a variety of laws and regulations that govern the patenting, testing, safety, efficacy and marketing of drugs.
These terms are used frequently in the pharmaceutical industry:

**Biologics** are bacterial and viral vaccines, antigens, antitoxins and analogous products, serums, plasmas and other blood derivatives for therapeutically protecting or treating humans and animals.

**Bulks** are active drug substances used to manufacture dosage-form products, process medicated animal feeds or compound prescription medications.

**Diagnostic agents** assist the diagnosis of diseases and disorders in humans and animals. Diagnostic agents may be inorganic chemicals for examining the gastrointestinal tract, organic chemicals for visualizing the circulatory system and liver and radioactive compounds for measuring the function of organ systems.
Drugs are substances with active pharmacological properties in humans and animals. Drugs are compounded with other materials, such as pharmaceutical necessities, to produce a medicinal product.

Ethical pharmaceuticals are biological and chemicals agents for preventing, diagnosing or treating disease and disorders in humans or animals. These products are dispensed by prescription or approval of a medical, pharmacy or veterinary professional.

Excipients are inert ingredients which are combined with drug substances to create a dosage form product. Excipients may affect the rate of absorption, dissolution, metabolism and distribution in humans or animals.
**PHARMACEUTICAL INDUSTRY**

*Over-the-counter pharmaceuticals* are drug products sold in a retail store or pharmacy which do not require a prescription or the approval of a medical, pharmacy or veterinary professional.

*Pharmacy* is the art and science of preparing and dispensing drugs for preventing, diagnosing or treating diseases or disorders in humans and animals.

*Pharmacokinetics* is the study of metabolic processes relating to the absorption, distribution, biotransformation, and elimination of a drug in humans or animals.

*Pharmacodynamics* is the study of drug action relating to its chemical structure, site of action, and the biochemical and physiological consequences in humans and animals.
The pharmaceutical industry is an important component of health care systems throughout the world; it is comprised of many public and private organizations that discover, develop, manufacture and market medicines for human and animal health.

The pharmaceutical industry is based primarily upon the scientific research and development (R&D) of medicines that prevent or treat diseases and disorders. Drug substances exhibit a wide range of pharmacological activity and toxicological properties.

Modern scientific and technological advances are accelerating the discovery and development of innovative pharmaceuticals with improved therapeutic activity and reduced side effects.
Molecular biologists, medicinal chemists and pharmacists are improving the benefits of drugs through increased potency and specificity. These advances create new concerns for protecting the health and safety of workers within the pharmaceutical industry.

Academic, government and industry scientists, practicing physicians and pharmacists, as well as the public, influence the pharmaceutical industry. Health care providers (e.g., physicians, dentists, nurses, pharmacists and veterinarians) in hospitals, clinics, pharmacies and private practice may prescribe drugs or recommend how they should be dispensed. Government regulations and health care policies on pharmaceuticals are influenced by the public, advocacy groups and private interests. These complex factors interact to influence the discovery and development, manufacturing, marketing and sales of drugs.
The pharmaceutical industry is largely driven by scientific discovery and development, in conjunction with toxicological and clinical experience (see figure 1).

Major differences exist between large organizations which engage in a broad range of drug discovery and development, manufacturing and quality control, marketing and sales and smaller organizations which focus on a specific aspect. Most multinational pharmaceutical companies are involved in all these activities; however, they may specialize in one aspect based upon local market factors. Academic, public and private organizations perform scientific research to discover and develop new drugs.
The pharmaceutical industry requires large amounts of capital investment due to the high expenses associated with R&D, regulatory approval, manufacturing, quality assurance and control, marketing and sales. Many countries have extensive government regulations affecting the development and approval of drugs for commercial sale. These countries have also strict requirements for good manufacturing practices to ensure the integrity of drug manufacturing operations and the quality, safety and efficacy of pharmaceutical products.
RESEARCH AND PRODUCTION OF THE MOLECULE

RESEARCH LABORATORIES
- Synthesis
- Fermentation
- Extraction

PHARMACEUTICAL AND TOXICOLOGICAL LABORATORIES
- Animal department
- Histology
- Histochemistry
- Microbiology
- Radioisotopes
- Mutagenesis
- Pharmacodynamics
- Physical and chemical analyses

Pilot-plant production of the pharmacologically active substance → Industrial production of the pharmaceutically active substance

Quality control

Pharmaceutical engineering → Industrial production of the pharmaceutical product
Many different biological and chemical agents are discovered, developed and used in the pharmaceutical industry.

Some manufacturing processes in the pharmaceutical, biochemical and synthetic organic chemical industries are similar; however, the greater diversity, smaller scale and specific applications in the pharmaceutical industry are unique.

Since the primary purpose is to produce medicinal substances with pharmacological activity, many agents in pharmaceutical R&D and manufacturing are hazardous to workers. Proper control measures must be implemented to protect workers from industrial chemicals and drug substances during many R&D, manufacturing and quality control operations.
The pharmaceutical industry uses biological agents (e.g., bacteria and viruses) in many special applications, such as vaccine production, fermentation processes, derivation of blood-based products and biotechnology.

Biological agents have unique pharmaceutical applications.

Chemical agents may be categorized as industrial chemicals and drug-related substances.
Industrial chemicals are used in researching and developing active drug substances and manufacturing bulk substances and finished pharmaceutical products.

Organic and inorganic chemicals are raw materials, serving as reactants, reagents, catalysts and solvents.

The use of industrial chemicals is determined by the specific manufacturing process and operations.

Many of these materials may be hazardous to workers. Since worker exposures to industrial chemicals may be hazardous, occupational exposure limits, such as threshold limit values (TLVs) have been established by government, technical and professional organizations.
Pharmacologically active substances (drug-related substances) may be categorized as natural products and synthetic drugs.

- Natural products are derived from plant and animal sources, while synthetic drugs are produced by microbiological and chemical technologies. Antibiotics, steroid and peptide hormones, vitamins, enzymes, prostaglandins and pheromones are important natural products.

- Scientific research is focusing increasingly on synthetic drugs due to recent scientific advances in molecular biology, biochemistry, pharmacology and computer technology.
LIST OF THE PRINCIPAL PHARMACEUTICAL AGENTS

1) **Central nervous system**
   a) Analgesics; Acetaminophen, Salicylates
   b) Anaesthetics; General and local
   c) Anticonvulsants; Barbituates, Benzodiazepine
   d) Migraine preparations; Beta adrenergic blocking agents, Serotonin receptor antagonists
   e) Narcotics; Opiates
   f) Psychotherapeutics; Antianxiety agents, Antidepressants
   g) Sedatives and hypnotics; Barbituates, Benzodiazepine
2) **Renal and cardiovascular system**
   
a) Antidiabetics; Biguanides, Glycosidase inhibitors, Insulins,

b) Cardioprotective agents; Adrenergic blockers, Stimulants, Angiotensin inhibitors, Antiarrhythmics, Calcium channel blockers, Diuretics, Vasodilators, Vasodepressors

3) **Gastrointestinal system**
   
a) Gastrointestinal agents; Antacids, Antiflatulents, Antidiarrhoeals, Antiemetics, Antispasmodics, Laxatives, Prostaglandins
4) **Anti-infectives and target organs**

a) Systemic anti-infectives; AIDS therapies, Amebicides, Anthelmintics, Antibiotics, Antifungals, Antimalarials, Sulphonamides, Cephalosporins, penicillins, tetracyclines, etc.

b) Respiratory agents;

c) Skin and mucous membrane agents; Acne preparations, Allergans, Anti-infectives, Burn preparations

d) Urinary tract agents; Anti-infectives, Antispasmodics

e) Vaginal preparations; Antifungals
5) **Immune system**
   
a) Analgesics; Non-steroidal anti-inflammatory agents -(NSAIDs)
   
b) Biological response modifiers; Alpha proteinase inhibitors, Antitoxins, Immune serums, Toxoids
   
c) Antifibrosis therapy
   
d) Immunodilators and immuno-suppressives
   
e) Multiple sclerosis management
6) **Chemotherapy;** Antineoplastics

7) **Blood and blood-forming organs;** Blood modifiers

8) **Endocrine system;** Diagnostics, Hormones, Prostaglandins
Pharmaceutical manufacturing operations may be categorized as basic production of bulk drug substances and pharmaceutical manufacturing of dosage form products.
Basic production of bulk drug substances may employ three major types of processes: fermentation, organic chemical synthesis, and biological and natural extraction.

These manufacturing operations may be discrete batch, continuous or a combination of these processes.

Antibiotics, steroids and vitamins are produced by fermentation, whereas many new drug substances are produced by organic synthesis.

Historically, most drug substances were derived from natural sources such as plants, animals, fungi and other organisms. Natural medicines are pharmacologically diverse and difficult to produce commercially due to their complex chemistry and limited potency.
1. FERMENTATION

- **Fermentation** is a biochemical process employing selected micro-organisms and microbiological technologies to produce a chemical product.
- Batch fermentation processes involve three basic steps: inoculum and seed preparation, fermentation, and product recovery or isolation.
- Inoculum preparation begins with a spore sample from a microbial strain. The strain is selectively cultured, purified and grown using a battery of microbiological techniques to produce the desired product. The spores of the microbial strain are activated with water and nutrients in warm conditions. Cells from the culture are grown through a series of agar plates, test tubes and flasks under controlled environmental conditions to create a dense suspension.
- The cells are transferred to a seed tank for further growth. The seed tank is a small fermentation vessel designed to optimize the growth of the inoculum. The cells from the seed tank are charged to a steam sterilized production fermenter.

- Sterilized nutrients and purified water are added to the vessel to begin the fermentation. During aerobic fermentation, the contents of the fermenter are heated, agitated and aerated by a perforated pipe, maintaining an optimum air flow rate and temperature.

- After the biochemical reactions are complete, the fermentation broth is filtered to remove the micro-organisms, or mycelia. The drug product, which may be present in the filtrate or within the mycelia, is recovered by various steps, such as solvent extraction, precipitation, ion exchange and absorption.
Solvents used for extracting the product generally can be recovered; however, small portions remain in the process wastewater, depending upon their solubility and the design of the process equipment.

*Precipitation* is a method to separate the drug product from the aqueous broth. The drug product is filtered from the broth and extracted from the solid residues. Copper and zinc are common precipitating agents in this process. Ion exchange or adsorption removes the product from the broth by chemical reaction with solid materials, such as resins or activated carbon. The drug product is recovered from the solid phase by a solvent which may be recovered by evaporation.
2. CHEMICAL SYNTHESIS

- Chemical synthesis processes use organic and inorganic chemicals in batch operations to produce drug substances with unique physical and pharmacological properties.
- Typically, a series of chemical reactions are performed in multi-purpose reactors and the products are isolated by extraction, crystallization and filtration.
- The finished products are usually dried, milled and blended.
- Organic synthesis plants, process equipment and utilities are comparable in the pharmaceutical and fine chemical industries.
- **Pharmaceutical chemistry** is complex with multi-step processing, where the product from one step becomes a starting material for the next step, until the finished drug product is synthesized.

- **Bulk chemicals** which are intermediates of the finished product may be transferred between organic synthesis plants for various technical, financial and legal considerations. Most intermediates and products are produced in a series of batch reactions on a campaign basis.

- Manufacturing processes operate for discrete periods of time, before materials, equipment and utilities are changed to prepare for a new process.

- Many organic synthesis plants in the pharmaceutical industry are designed to maximize their operating flexibility, due to the diversity and complexity of modern medicinal chemistry. This is achieved by constructing facilities and installing process equipment that can be modified for new manufacturing processes, in addition to their utility requirements.
Multi-purpose reactors are the primary processing equipment in chemical synthesis operations. They are reinforced pressure vessels with stainless, glass or metal alloy linings. The nature of chemical reactions and physical properties of materials (e.g., reactive, corrosive, flammable) determine the design, features and construction of reactors. Multi-purpose reactors have external shells and internal coils which are filled with cooling water, steam or chemicals with special heat-transfer properties. The reactor shell is heated or cooled, based upon the requirements of the chemical reactions. Multi-purpose reactors have agitators, baffles and many inlets and outlets connecting them to other process vessels, equipment and bulk chemical supplies. Temperature-, pressure- and weight-sensing instruments are installed to measure and control the chemical process in the reactor. Reactors may be operated at high pressures or low vacuums, depending upon their engineering design and features and the requirements of the process chemistry.
DIAGRAM OF A CHEMICAL REACTOR IN ORGANIC SYNTHESIS

3. BIOLOGICAL AND NATURAL EXTRACTION

- Large volumes of natural materials, such as plant and animal matter, may be processed to extract substances which are pharmacologically active. In each step of the process, the volumes of materials are reduced by a series of batch processes, until the final drug product is obtained. Typically, processes are performed in campaigns lasting a few weeks, until the desired quantity of finished product is obtained. Solvents are used to remove insoluble fats and oils, thereby extracting the finished drug substance. The pH (acidity) of the extraction solution and waste products can be adjusted by neutralizing them with strong acids and bases. Metal compounds frequently serve as precipitating agents, and phenol compounds as disinfectants.