Introduction to Drugs and Pharmacy

Summarized by Dr. Mazen Rajab

Ref. Pharmaceutical dosage forms and drug delivery systems, Ansel's 9th ed 2011 pp 1-25

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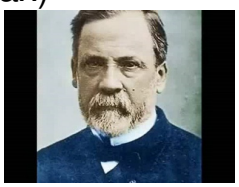
- Introduction
- The heritage of pharmacy
- Drug standard
- Drug regulation and control
- The pharmacist's contemporary role

Introduction

- Drug: an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animal.
- Pharmacology
  - Diversity of drug effects
  - Selectivity of drug use

Introduction

- Drug discovery
  - New **A**ctive **P**harmaceutical **I**ngredient (API) may be derived from:
    - Plant (salicylic acid) or animal sources.
    - Byproducts of microbial growth (Penicillin, Alexander Fleming)
    - Chemical synthesis (Paracetamol)
    - Molecular modification (Aspirin)
    - Biotechnology (Vaccines) (Edward Jenner, smallpox); (Louis Pasteur, anthrax)
    - Bioinformatics



Introduction

- Drug Development
  - Chemical and physical characterization.
  - Biological information:
    - Basic pharmacology, mechanism and site of action.
    - Toxicological features (LD_{50} level).
    - Drug Absorption, Distribution, Metabolism and Elimination (ADME).
    - Drug minimum and maximum doses (Therapeutic window).
    - Effect on fetus and pregnant animal (Thalidomide) or its ability to pass to a nursing baby by breast milk.
    - Selection of the most effective routes of administration (oral, rectal, parenteral, topical).

Introduction

(Drug Development)

- Dosages recommended for varying ages (neonatal, children, adults, geriatrics…).
- It has been said that the only difference between drug and poison is the dose.

– Selection of drug dosage form to facilitate administration of the drug by selected route with selected dose. Examples:
  - Tablets,
  - Capsule,
  - Creams...

Introduction

(Drug Development)

– Drug dosage form design, development, production and use are the product of application of the pharmaceutical sciences which is the blending of the basic, applied and clinical sciences with the pharmaceutical technology.

– Drug dosage form contains APIs and non APIs. The non API are called non therapeutic, pharmaceutical ingredients or excipients that wide range of functions (anti-microbial preservatives, solvents and fillers….)

The heritage of pharmacy

- Pre-historic
  - Drugs, in the form of vegetation and minerals have existed as long as humans.
  - Disease was belived to be caused by the entrance of demons or evil spirits into body.
- The first apothecary
  - It was in the preparation of the medicinal materials that the art of the apothecary originated.
  - In Homeric epics, the term *pharmakon* form which our word pharmacy was derived, connotes a charm or a drug that can be used for good or for evil.

The heritage of pharmacy

- Early drugs
  - Ebers papyrus (1600 BC) Egyptian long scroll contains 800 formulas where 700 drugs were mentioned. The drug are chiefly botanical, miniral and animal.
- Introduction of the scientific view point
  - Hippocrates (Father of Medicine). He wrote Hippocratic oath of ethical behavior for the healing professions and he described hundreds of drugs.
  - Role of our countries

Drug Standards

- The need for uniform standards to ensure quality
  - The term Pharmacopeia comes from *pharmakon (drug)* and *poiein (to make)*
  - The United States Pharmacopeia and the National Formulary (USP-NF)
  - Homeopathic Pharmacopeia of the United States (HPUS)
  - International Pharmacopeia (IP) by WHO.
  - British Pharmacopeia (BP)
  - European Pharmacopeia (Euro. Ph.)
  - Good Manufacture Practices (GMP)
  - International Organization for Standardization (ISO): ISO 9000 to ISO 9004.

Drug Standards

- United States Pharmacopeial Convention constitution has delegates that represent:
  - Educational institutions.
  - Professional and scientific organization.
  - Divisions of governmental bodies.
  - Non-United States international organizations and pharmacopeial bodies.
  - Persons who posses special scientific competence or knowledge of emerging technologies
  - Public members
- Board of trustees: formed from 7 elected members
  - 2 medical sciences.
  - 2 pharmaceutical sciences
  - and 1 public member

Drug Standards

- In 1980 the first combined compendium USP XX and NF XV where:
  - USP contains all monographs on therapeutically API
  - NF contains all monographs on Excipients
- In 2005 the first edition of the *USP pharmacists' Pharmacopeia* for practicing pharmacists

Drug Standards

- USP monograph for API:
  - Official title
  - Graphic or structural formula
  - Empirical formula
  - Molecular weight
  - Established chemical names
  - Chemical Abstracts Service (CAS) registry number.
  - Statement of chemical purity.
  - Cautionary statement (toxic nature)
  - Packaging and storage
  - Labeling
  - USP Reference standards
  - Identification (Melting range, Infrared Absorption, ultraviolet Absorption…)
  - Assay

Drug Standards

- USP monograph for product:
  - Official title.
  - API content of each product unit
  - Packaging and storage
  - Labeling
  - USP Reference standards
  - Identification
  - Dissolution test
  - Uniformity of dosage units
  - Assay

Drug Regulation and Control

- The federal Food and Drug Act (Wiley Act) of 1906
  - Harvey Wiley, US Department of Agriculture, is the father of: Food and Drug Administration (FDA).
  - Prohibition of interstate transport of drugs, that are not listed on US Pharmacopoeia or National Formulary.
- The federal Food, Drug and cosmetic Act of 1938
  - Elixir of sulfanilamide was prepared with Diethylene glycol a highly toxic anti freeze solutions.100 persons died.
  - The creation of FDA.
  - Prohibition of distribution and using of any new drug or drug product without the approval of FDA
  - New-Drug Application (NDA)

Drug Regulation and Control

- Durham-Humphrey Amendment 1952
  - Drug Over the Counter (OTC).
  - Drug Rx Only
- Kefauver-Harris Amendments of 1962
  - In 1960 the tragedy of thalidomide
  - Investigational New-Drug application (IND) before the drug may be clinically tested on human subjects.
  - Clinical trials to show the safety and effectiveness of the API or the product
  - NDA

Drug Regulation and Control

- Comprehensive Drug Abuse Prevention and control Act of 1970
  - Schedule I: Drugs with no accepted medical use or with high potential for abuse (heroin)
  - Schedule II: Drugs with accepted medical use and with high potential for abuse (morphine)
  - Schedule III: Drugs with accepted medical use and with moderated potential for abuse (codeine)
  - Schedule IV: Drugs with accepted medical use and with low potential for abuse (diazepam)
  - Schedule V: Drugs with accepted medical use and with very low potential for abuse (dihydrocodeine)

Drug Regulation and Control

- FDA pregnancy categories (1979)
  - Category A: In animal and pregnant women No risk to the fetus in the first trimester of pregnancy and in later trimesters.
  - Category B: In animal no risk to the fetus, no well-controlled studies for pregnant women.
  - Category C: In animal there is risk to the fetus and no well-controlled studies for pregnant women. But potential benefits may warrant pregnant women
  - Category D: Positive evidence of human fetal risk. But potential benefits may warrant pregnant women.
  - Category X: In animals or humans, fetal abnormalities and the risks involved is clearly outweigh potential benefits for pregnant women
- Teratogenic potential: stage of pregnancy and amount of medication.
- In pregnant or Breast-feeding-patient must be counseled about adverse effects.
- **Black box warnings (BBWs)** are the FDA's strongest labeling requirements for high-risk medicines.

Drug Regulation and Control

- Drug listing Act of 1972 :
  - All products must have National Drug Code (NDC) number to identify company, drug, package.
- Drug price competition and patent term restoration Act of 1984:
  - For generic drugs (no patent), Abbreviated New-Drug Application (ANDA) without NDA.
  - Drug under patented have 20 years of patents + time of FDA review of NDA + ½ time of testing phase.

Drug Regulation and Control

- Prescription drug marketing Act of 1987:
  - Prohibits the re-importation of USA products.
  - Sales restriction of product samples or products bought by health care or charitable institutions.
  - Distribution of drug samples only to practitioners licensed or to prescribe such drug.
  - Only authorized Wholesale distributors.
- Dietary supplements health and education Act of 1994
  - No need for NDA but it forbids the indication of prevent or cure a specific disease. A disclaimer must appear on the product :" this product is not intended to diagnose, treat, cure or prevent any disease".

Drug Regulation and Control

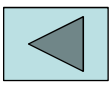
- The FDA and the food and drug administration modernization Act 1997
  - Sets policies, establishes standards, issues guidelines, enforces rules and regulations.
  - Monitors for regulatory compliance.
  - Establishes product labeling requirements.
  - Acts as the government's gatekeeper.
- Code of Federal Regulations and the federal register (CFR)
- Drug product recall
  - Class I: Serious adverse health consequences or death.
  - Class II: Temporary or reversible adverse health consequences.
  - Class III: Not likely to cause adverse health consequences.

The pharmacist's contemporary role

- Code of ethics of American Pharmacists Association (APhA)
  - Pharmacists are health professionals who assist individuals in making the best use of medication. A pharmacist:
    - Respects the covenantal relationship between the patient and pharmacist.
    - Promotes the good of every patient in a caring, compassionate and confidential manner.
    - Maintains professional competence.
    - Seeks justice in the distribution of health resources.

Therapeutic window

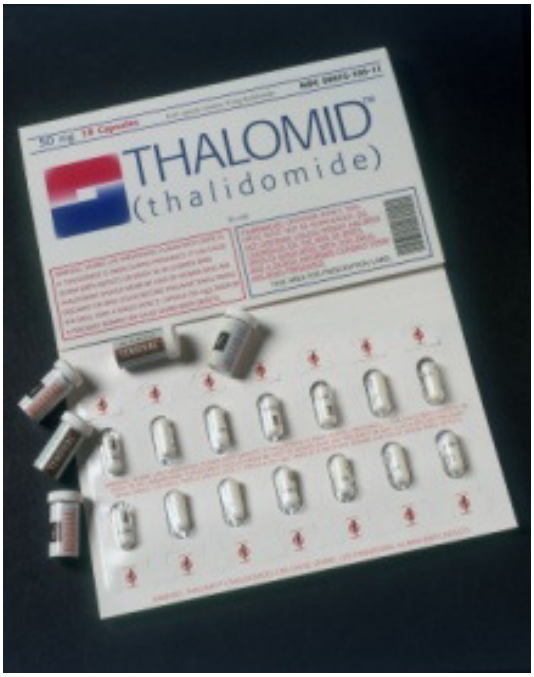
- The term therapeutic window refers to the range of doses of a drug that are actually effective in treating a particular disease. Doses below the therapeutic window are too weak to have any effect; doses above the window cause unacceptable side-effects.
- More specifically, it is the range between the ED_{50} and the starting point of TD_{50}. It is believed that this index can help to avoid most of the potential side effects.
- ED: The “effective dose” is the dose of drug that produces a therapeutic response effect.
- ED_{50} :The "median effective dose" is the amount that will produces the desired intensity of effect in 50% of the individuals tested.
- TD_{50} : The “median toxic dose” is the amount that will produces a defined toxic effect in 50% of the individuals tested.
- The relationship between the desired and undesired effects of a drug is expressed as the Therapeutic index = TD_{50}/ED_{50}

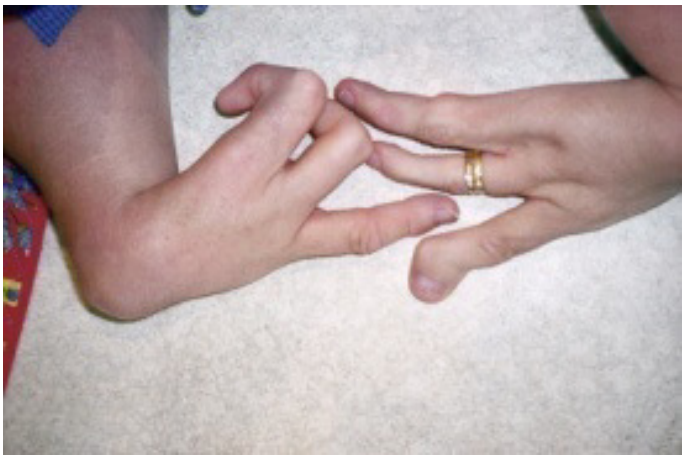


Thalidomide

- The thalidomide disaster is one of the darkest episodes in pharmaceutical research history. The drug was marketed as a mild sleeping pill safe even for pregnant women. However, it caused **thousands of babies worldwide** to be born with malformed limbs. The damage was revealed in **1962**. Before then, every new drug was seen as beneficial. Now there was suspicion and rigorous testing.
- Thalidomide was developed in the 1950s by the West German pharmaceutical company Chemie Grünenthal GmbH. It was an anticonvulsive drug, but instead it made users sleepy and relaxed. It seemed a perfect example of newly fashionable tranquilisers.
- During patenting and testing, scientists realized it was practically impossible to achieve an **LD_{50}** level, or deadly overdose, of the drug. Animal tests did not include tests looking at the effects of the drug during pregnancy. The apparently harmless thalidomide was licensed in **July 1956** for prescription-free over-the-counter sale in Germany and most European countries. The drug also reduced morning sickness, so it became popular with pregnant women.
- WHO consider Thalidomide as standard treatment for fever and painful skin lesions associated with erythema nodosum leprosum.

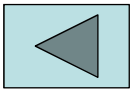
Thalidomide





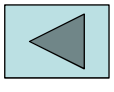
LD_{50} level

- LD_{50} is the dose of any substance tested required to kill half the number (50%) of test animals. The test shows how much of a substance must be taken before it becomes deadly.
- For example, a rat must be fed 50 mg of nicotine per kilo of bodyweight before it dies.
- Various forms of LD_{50} test include feeding the substance by mouth, applying it on the skin, and injecting it into veins, muscle tissue or the body cavity.
- Animal rights activists oppose LD_{50} animal testing because the death from poisoning is slow and painful. The LD_{50} test is also controversial among scientists because of doubts about the usefulness and reliability of the results it gives. Some types of LD_{50} test, especially oral, have been phased out or banned in the UK.



Aspirin

- Salicylic acid: Hippocrates, who lived sometime between 460 BC and 377 BC, left historical records describing the use of powder made from the bark and leaves of the willow tree to help alleviate headaches, pains, and fevers.
- The synthesis of aspirin is classified as an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns salicylic acid's hydroxyl group into an ester group (R-OH → R-OCOCH3). This process yields aspirin and acetic acid, which is considered a byproduct of this reaction. Small amounts of sulfuric acid (and occasionally phosphoric acid) are almost always used as a catalyst.



Amoxicillin Capsules

Amoxicillin Capsules

» Amoxicillin Capsules contain the equivalent of not less than 90.0 percent and not more than 120.0 percent of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$).

Packaging and storage— Preserve in tight containers, and store at controlled room temperature.

Add the following:

▲**Labeling—** When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.▲ USP40

USP Reference standards ⟨ 11 ⟩ —
USP Amoxicillin RS.

Identification— Prepare a test solution containing the equivalent of 4 mg of amoxicillin per mL by adding 0.1 N hydrochloric acid to powder from Amoxicillin Capsules. Prepare a Standard solution of *USP Amoxicillin RS* in 0.1 N hydrochloric acid containing 4 mg per mL. Use within 10 minutes after preparation. Apply separately 5 µL of each solution on a thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel mixture (see *Chromatography* ⟨ 621 ⟩).

Dissolution ⟨ 711 ⟩ —

▲TEST 1—▲ USP40

Medium: water; 900 mL.

Apparatus 1: 100 rpm, for Capsules containing 250 mg.

Apparatus 2: 75 rpm, for Capsules containing 500 mg.

Time: 60 minutes.

Procedure— Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under

Uniformity of dosage units ⟨ 905 ⟩ **:** meet the requirements.

Water, *Method I* ⟨ 921 ⟩ **:** not more than 14.5%.

Assay—

Diluent, Mobile phase, Standard preparation, and *Chromatographic system*— Prepare as directed in the *Assay* under *Amoxicillin*.

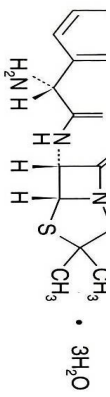
Assay preparation— Remove, as completely as possible, the contents of not fewer than 20 Capsules, and weigh accurately. Mix the combined contents, and transfer an accurately weighed quantity, equivalent to about 200 mg of anhydrous amoxicillin, to a 200-mL volumetric flask, add *Diluent* to volume, and mix. Sonicate if necessary to ensure complete dissolution. Pass a portion of this solution through a suitable filter having a 1-µm or finer porosity, and use the filtrate as the *Assay preparation*. Use this solution within 6 hours.

Procedure— Proceed as directed for *Procedure* in the *Assay* under *Amoxicillin*. Calculate the quantity, in mg, of amoxicillin ($C_{16}H_{19}N_3O_5S$) in the portion of Capsules taken by the formula:

$$0.2CP(r_u / r_s)$$

in which the terms are as defined therein.

Amoxicillin



$C_{16}H_{19}N_3O_5S \cdot 3H_2O$ 419.45

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino-3, 3-dimethyl-7-oxo-, trihydrate 2*S*-[2α,[5α,6β(*S**)]]-. (2*S*,5*R*,6*R*)-6-[(*R*)-(−)-2-Amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid trihydrate [61336-70-7].

Anhydrous 365.41 [26787-78-0].

Amoxicillin contains not less than 900 µg and not more than 1050 µg of $C_{16}H_{19}N_3O_5S$ per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, at controlled room temperature.

Labeling—Where it is intended for use in preparing injectable dosage forms, the label states that it is intended for veterinary use only and that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. Label all other Amoxicillin to indicate that it is to be used in the manufacture of nonparenteral drugs only.

USP Reference standards [11]—*USP Amoxicillin RS*. *USP Endotoxin RS*.

Identification, *Infrared Absorption* ⟨197K⟩.

Crystallinity [695]: meets the requirements.

pH [791]: between 3.5 and 6.0, in a solution containing 2 mg per mL.

Water, *Method I* [921]: between 11.5% and 14.5%.

Dimethylaniline [223]: meets the requirement.

Other requirements—Where the label states that Amoxicillin is sterile, it meets the requirements for *Sterility and*

solution of potassium hydroxide to a pH of 5.0±0.1.

Mobile phase—Prepare a suitable filtered mixture of *Diluent* and acetonitrile (96:4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). Decrease the acetonitrile concentration to increase the retention time of amoxicillin.

Standard preparation—Dissolve an accurately weighed quantity of USP Amoxicillin RS quantitatively in *Diluent* to obtain a solution having a known concentration of about 1.2 mg per mL. Use this solution within 6 hours.

Assay preparation—Transfer about 240 mg of Amoxicillin, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix. Use this solution within 6 hours.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the capacity factor, k', is between 1.1 and 2.8, the column efficiency is not less than 1700 theoretical plates, the tailing factor is not more than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of $C_{16}H_{19}N_3O_5S$ per mg of the Amoxicillin taken by the formula:

$$200(CP/W)(r_u/r_s),$$

in which C is the concentration, in mg per mL, of USP Amoxicillin RS in the *Standard preparation*, P is the stated amoxicillin content, in µg per mg, of USP Amoxicillin S, W is the quantity, in mg, of Amoxicillin taken to prepare

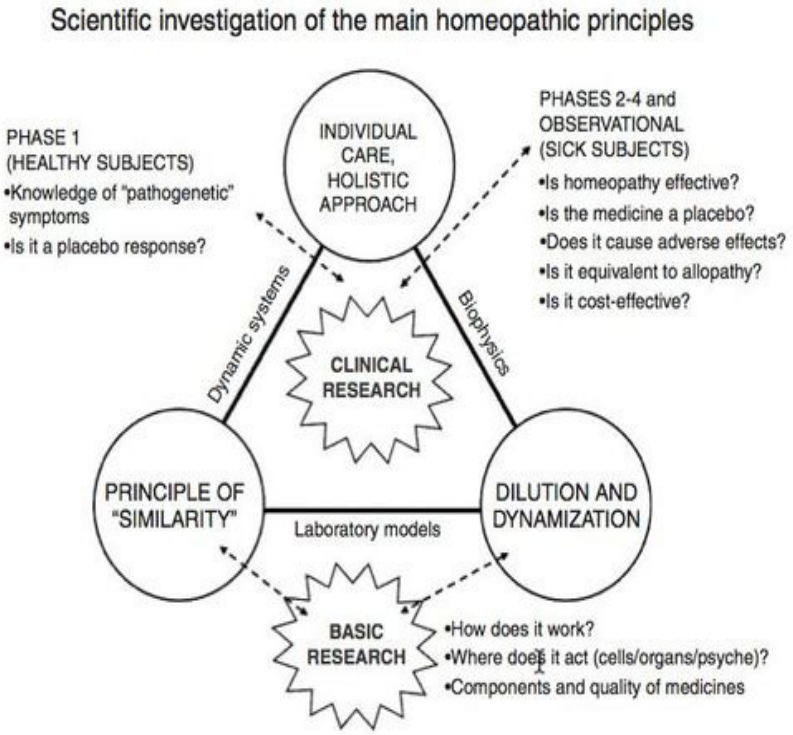


Figure 1. The three tenets of homeopathy. Similarity: healing is achieved by taking a drug that proved by healthy individuals have yielded symptoms and signs very similar to those of the patients. Dilution and dynamization: homeopathy uses diluted and 'dynamized' drugs: dilution followed by succussion should increase the drug 'potency'. Individualization: homeopathic approach is personalized, is a 'holistic' method of diagnosis and of prescription. These three strictly related aspects of homeopathy can become objects of scientific investigation.

- # Top Homeopathic Remedies for Kidney Disease
- **Ammonium carbonicum:** mental sluggishness, fatigue, turbid, bloody, scanty or fetid urine and painful urination.
- **Apis mellifica:** kidney inflammation, urine suppression and general edema.
- **Arsenic album:** scanty and burning urination, difficult urination and nephritis.
- **Aurum metallicum:** urine with mucous sediment and painful retention of urine.
- **Belladonna:** inflamed kidneys.
- **Cannabis indica:** urinary tract infections.
- **Chelidoniumm majus:** copious urination, pale white urine and frequent night urination.
- **Cuprum Arsenicosum:** painful urination, discolored urine and kidney function.
- **Cuprum Metallicum:** clear watery urine, sharp pain in urethra, bed-wetting, urine suppression and frequent urination of fetid and viscid urine.
- **Glonoin:** kidney inflammation and frequent night urination and helonia's rubrics are anemia, irritability, kidney inflammation and dullness.
- **Juniperus Virginiana:** heaviness in kidney region and water retention.
- **Opium:** general edema, urine suppression, uremic convulsions, body sluggishness, black stool and white urine.
- **Phosphorous:** uremia, turbid urine with sedimentation, kidney swelling and extreme fatigue.
- **Sanicula Aqua:** kidney stones and inflammation and bladder irritation.
- **Terebinthina:** kidney and urinary tract inflammation and discolored urine.