CHAPTER 3:
NUTRACEUTICALS
DOSAGE FORM

INTRODUCTION
LEARNING OBJECTIVES

The objectives of this unit are to:

• Understand nutraceutical dosage form.

• Understand the dosage form design consideration
LEARNING OUTCOMES

After completing this unit, student should be able to:

• Identify the dosage form design based on pharmaceutical and formulation considerations

• Identify the dosage form design based on biopharmaceutics considerations
INTRODUCTION

• How drugs move around the body and how quickly this movement occurs.

• During this course many of the processes which control the absorption, distribution, metabolism, and excretion of drugs will be discussed, qualitatively (biopharmaceutics) and quantitatively (pharmacokinetics).

• Biopharmaceutics is the area of study embracing the relationship between the physical, chemical, and biological sciences as they apply to drugs, dosage forms, and to drug action.

• For a drug to exert its biological effect, it must be transported by the body fluids, traverse the required biological membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, penetrate in adequate concentration to the sites of action, interact in a specific fashion, causing an alteration of cellular function.
CHAPTER 3: NUTRACEUTICALS

DOSAGE FORM

3.1: DOSAGE FORM DESIGN: PHARMACEUTICAL AND FORMULATION CONSIDERATIONS
INTRODUCTION

• Nutraceuticals are also biologically active phytochemical substances obtained from plants and natural minerals and are major formulation products for industry.

• Nutraceutical manufacturers face some hurdles for formulation consideration since the idea behind nutraceuticals is to achieve a desirable therapeutic result, without the side effects often associated with pharmaceuticals.

• One problem is the drug content and drug uniformity in the dosage forms since nutraceuticals are a cluster of chemical entities and it will be comparatively difficult to identify and quantify all the ingredients in the products.

• In such situations, at least one major ingredients can be identified and quantified to ensure the uniform distribution of the product through the matrix.
PHAMACEUTIC INGREDIENTS CONSIST

solubilize

Stabilize

eмуlify

dilute

suspend

thicken

preserve

color

flavor

PHAMACEUTIC INGREDIENTS
The general area of study concerned with the formulation, manufacture, stability, and the effectiveness of pharmaceutical dosage forms. Physical, chemical, and biological characteristics are also considered compatible.
A drug products:

- stable
- efficacious
- attractive
- easy to administer
- safe
- quality control
Pharmaceutical Technology

Definition:

- The application of scientific knowledge or technology to pharmacy, pharmacology, and the pharmaceutical industry. It includes methods, techniques, and instrumentation in the manufacture, preparation, compounding, dispensing, packaging, and storing of drugs and other preparations used in diagnostic and determinative procedures and in the treatment of patients.

Reference: http://dictionary.sensagent.com
Why we need formulation considerations?

Besides providing the mechanism for the safe and convenient delivery of accurate dosage / formulation, dosage forms are needed for additional reasons:

1. Protection from oxygen and humidity (coated tablets, sealed ampuls)
2. Protection from gastric acid after oral administration (enteric-coated tablets)
3. To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups)
4. Liquid preparation for insoluble or unstable in the desired vehicle to reduce suspension
5. To provide clear liquid dosage forms of substances (syrups, solutions)
Why we need formulation considerations?

6. To provide rate-controlled drug action (various controlled-release tablets, capsules and suspensions)

7. To provide topical drug action from topical administration sites (ointments, creams, transdermal patches, ophthalmic, ear, and nasal preparations)

8. To provide for the insertion of a drug into one of the body’s orifices (e.g., rectal or vaginal suppositories)

9. To provide for the placement of drugs directly into the bloodstream or into body’s tissues (e.g., injections)

10. To provide for topical drug action through inhalation therapy (e.g., inhalants and inhalation aerosols)
Before the formulation of a drug substance into a dosage form, it is essential that it will be chemically and physically characterized:

- Physical description
- Pre-formulation studies
- Polymorphism
- Particle size
- The phase rule
- Microscopic examination
- Melting point depression
- Solubility
- Pre-formulation studies
- Partition coefficient
- Solubility and particle size
- Membrane permeability
- Dissolution
- Solubility and pH
Pre-formulation studies

1. Physical description

• The majority of drug substances in use today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution.

• A crystal or crystalline solid is a solid material whose constituent atoms, molecules, or ions are arranged in an orderly repeating pattern extending in all three spatial dimensions.

• An amorphous solid is a solid in which there is no long-range order of the positions of the atoms.
Pre-formulation studies

2. Microscopic examination
   - Microscopic examination of the raw drug substance is an important step in preformulation work.
   - It gives an indication of particle size and particle size range of the raw material as well as the crystal structure.

3. Melting point depression
   - A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a depressed melting point.
   - This phenomenon is commonly used to determine the purity of a drug substances before inclusion in the same dosage form.
Pre-formulation studies

4. Polymorphism

• An important factor on formulation is the crystal or amorphous form of the drug substance.

• Polymorphic forms usually exhibit different physical-chemical properties including melting point and solubility.

• The changes in crystal characteristics can influence bioavailability, chemical and physical stability, and have important implications in dosage form process functions.
Pre-formulation studies

5. Solubility

• A drug must possess some aqueous solubility for therapeutic efficacy.

• For a drug to enter the systemic circulation to exert a therapeutic effect, it must first be in solution.

• Relatively insoluble compounds often exhibit incomplete or erratic absorption.

• If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility.
TYPES OF STABILITY CONCERN PHARMACISTS

Chemical
- Each active ingredient retains its chemical integrity and labeled potency within the specified limits.

Physical
- The original physical properties, including appearance, uniformity, dissolution, and suspend ability are retained.

Microbiologic
- Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.

Therapeutic
- The therapeutic effect remains unchanged

Toxicologic
- No significant increase in toxicity occurs.
CHAPTER 3: NUTRACEUTICALS DOSAGE FORM

3.2: DOSAGE FORM DESIGN: BIOPHARMACEUTICS CONSIDERATIONS
INTRODUCTION

• Drugs are not generally given as a pure chemical but formulated into a finished dosage form (drug product). A formulated drug product usually includes the active drug substance and selected ingredients.

• A primary concern in biopharmaceutics is the bioavailability of drugs.

• Bioavailability refers to the measurement of the rate and extent of drug that reaches the systemic circulation.
INTRODUCTION

• The aim of biopharmaceutics is to adjust the delivery of drug from the drug product in such a manner as to provide optimal therapeutic activity and safety for the patient.

• The area of study which elucidates the time course of drug concentration in the blood and tissues is termed pharmacokinetics.

• It is the study of the kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic response in animals and man.

• Pharmacokinetics also may be applied in the study of interactions between drugs.
• Biopharmaceutics can be regarded as the study of the relationship between the physical, chemical and biological sciences applied to drugs, dosage forms and drug action.
Dosage forms available for different administration routes

Biopharmaceutical considerations including factors affecting the absorption the drug substances from different administrations routes.

Drug factors such as the physical and chemical properties of the drug substances.

Therapeutic considerations including consideration of the clinical indication to be threatened and patient factors.
Major biopharmaceutical considerations in the design of drug products:

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Key Points</th>
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</thead>
<tbody>
<tr>
<td>Pharmacodynamic consideration</td>
<td>- Therapeutic objective, toxic effect and adverse reactions.</td>
</tr>
<tr>
<td>Drug consideration</td>
<td>- Chemical and physical properties of drug.</td>
</tr>
<tr>
<td>Drug product consideration</td>
<td>- Pharmacokinetics of drug, bioavailability of drug, route of drug</td>
</tr>
<tr>
<td></td>
<td>administration, desired drug dosage from and desired dose of drug.</td>
</tr>
<tr>
<td>Patient consideration</td>
<td>- Compliance and acceptability of drug product</td>
</tr>
<tr>
<td>Manufacturing considerations</td>
<td>- Cost, availability of raw materials, stability and quality control.</td>
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# ROUTE OF ADMINISTRATION

<table>
<thead>
<tr>
<th>Administration route</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Solutions, syrups, suspensions, emulsions, gel, powders, granules, capsules, tablets</td>
</tr>
<tr>
<td>Rectal</td>
<td>Suppositories, ointments, creams, powders, solutions.</td>
</tr>
<tr>
<td>Topical</td>
<td>Ointments, creams, pastes, lotions, gels, solutions, topical aerosols, transdermal patches</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Injections (Solutions, suspensions, emulsion forms), implants, irrigation and dialysis solutions.</td>
</tr>
<tr>
<td>Respiratory/Lungs</td>
<td>Aerosols (Solutions, suspension, powder form), inhalations, sprays and gases.</td>
</tr>
</tbody>
</table>
1. ORAL ROUTE

- Oral dosage forms are intended usually for systematic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract.

2. RECTAL ROUTE

- Drug given rectally in suppository form.
- Suppositories are solid forms intended for introduction into body cavities. This route indicated for drug inactivated by the gastrointestinal fluid when given orally. Example, patient is vomiting or unconscious.
3. PARENTERAL ROUTE

- Injected by hollow needle into the body at various sites and to varying depths.

- Main parental routes: subcutaneous, intramuscular, intravenous preferred when rapid absorption is essential.

- Example: as emergency situation or patient unable to accept oral medication.

4. TOPICAL ROUTE

- Drugs are applied topically, that is to skin, mainly for local action.

- This route can also be used for systemic drug delivery.
5. RESPIRATORY ROUTE

- The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol mist or ultrafine solid particle form.
PHARMACOKINETIC

Definition:

- Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion.

- Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.
INTRODUCTION

What is Pharmacokinetics?

how the human body act on the drugs?

• Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. Intensity of effect is related to concentration of the drug at the site of action, which depends on its pharmacokinetic properties

• Pharmacokinetic properties of particular drug is important to determine the route of administration, dose, onset of action, peak action time, duration of action and frequency of dosing
RELATIONSHIP DYNAMIC & KINETICS

Dosage Regimen

Pharmacokinetics

Absorption
Distribution
Metabolism
Excretion

Concentration in Plasma

Pharmacodynamics

Concentration at the site of action

Effect
The Pharmacokinetic Process

**Absorption**
- Drug in dosage form
  - Release
- Drug in Solution

**Distribution - Storage**
- Site of Action
  - Bound ⇌ Free
- Storage Tissue
  - Free ⇌ Bound

**Biotransformation**
- FREE DRUG
- Protein Bound
- Metabolites

**Excretion**
- Urine
- Bile
- Faeces
- Sweat
- Saliva
The Pharmacokinetic Process
Biological Membrane - image
1. Absorption of Drugs

- Absorption is the transfer of a drug from its site of administration to the blood stream
- Most of drugs are absorbed by the way of passive transport
- Intravenous administration has no absorption
- Fraction of administered dose and rate of absorption are important
Factors affecting absorption

➢ Drug properties:
   lipid solubility, molecular weight, and polarity etc

• Blood flow to the absorption site
• Total surface area available for absorption
• Contact time at the absorption surface
• Affinity with special tissue

Routes of Administration (important):
2. Distribution of Drugs

- It is the passage of drug from the circulation to the tissue and site of its action.

- The extent of distribution of drug depends on its lipid solubility, ionization at physiological pH (dependent on pKa), extent of binding to plasma and tissue proteins and differences in regional blood flow, disease like CHF, uremia, cirrhosis.

- Movement of drug - until equilibration between unbound drug in plasma and tissue fluids.
3. Metabolism of drug (Biotransformation)

- What is biotransformation?
- Chemical alteration of the drug in the body
- Aim: to convert non-polar lipid soluble compounds to polar lipid insoluble compounds to avoid reabsorption in renal tubules
- Most hydrophilic drugs are less biotransformed and excreted unchanged – streptomycin, neostigmine and pancuronium etc.
- Biotransformation is required for protection of body from toxic metabolites
Results of Biotransformation

1. Active drug and its metabolite to inactive metabolites – most drugs (ibuprofen, paracetamol, chlormphenicol etc.)

2. Active drug to active product (phenacetin – acetminophen or paracetamol, morphine to Morphine-6-glucoronide, digitoxin to digoxin etc.)

3. Inactive drug to active/enhanced activity (prodrug) – levodopa - carbidopa, prednisone – prednisolone and enlpril – enlprilat)

4. No toxic or less toxic drug to toxic metabolites (Isonizide to Acetyl isoniazide)
Biotransformation - Classification

- **2 (two) Phases of Biotransformation:**
  - **Phase I** or Non-synthetic – metabolite may be active or inactive
  - **Phase II** or Synthetic – metabolites are inactive (Morphine – M-6 glucuronide is exception)
Factors affecting Biotransformation

- Factors affecting biotransformation
  - Concurrent use of drugs: Induction and inhibition
  - Genetic polymorphism
  - Pollutant exposure from environment or industry
  - Pathological status
  - Age
4. Excretion
Organs of Excretion

• Excretion is a transport procedure which the prototype drug (or parent drug) or other metabolic products are excreted through excretion organ or secretion organ.

• Hydrophilic compounds can be easily excreted.

• Routes of drug excretion
  – Kidney
  – Biliary excretion
  – Sweat and saliva
  – Milk
  – Pulmonary
Target Level Strategy

• Low safety margin drugs (anticonvulsants, antidepressants, Lithium, Theophylline etc.) – maintained at certain concentration within therapeutic range

• Drugs with short half-life (2-3 Hrs) – drugs are administered at conventional intervals (6-12 Hrs) – fluctuations are therapeutically acceptable

• Long acting drugs:
  – Loading dose: Single dose or repeated dose in quick succession – to attain target conc. Quickly
  – Maintenance dose: dose to be repeated at specific intervals
THANK YOU

NOOR MUHAMMAD SYAHRIN BIN YAHYA