PHARMACEUTICAL DOSAGE FORMS

Limitations on the direct clinical use of the active drug substances „as they are“:

- handling – difficult or impossible (low doses)
- accurate drug dosing – difficult or impossible
- administration – impractical
- environmental factors – negative impact on drug chemical instability
- degradation at the site of administration
- local irritations or injury
- unpleasant organoleptic qualities (taste, smell)
- no chance for modification of PK profile

Pharmaceutical preparations

- **Original pharmaceutical preparations**
  - full and very extensive pharmacological/ toxicological and pharmaceutical pre-clinical and clinical evaluation
  - the proof of effectiveness and safety
- **Generic pharmaceutical preparations**
  - can be released after the expiration of the patent protection of the original preparation
  - easier approval for clinical use due to the prior experience with the original preparation

Original vs. Generic preparations

- **Must be pharmaceutically equivalent:**
  - same active ingredient, dose, pharmaceutical dosage form, route of administration
- **Must be clinically bioequivalent:**
  - similar PK profile (Cmax, tmax, AUC are within 80-125 % range as compared with the original preparation)
- **Don’t have to be therapeutically equivalent:**
  - comparing directly the clinical effectiveness is not commonly required

Pharmaceutical preparations compounded individually

- prepared individually for a particular patient according to the physician's prescription in a pharmacy licensed for compounding
- individualization the pharmacotherapy when:
  - the drug in a particular dosage form is not commercially available
  - the extraordinary low or high dose is needed
  - patient is unable to use drug in its commercially available dosage form
  - allergy on a specific ingredients
- **lack of standardization**

PHARMACEUTICAL DOSAGE FORMS

- a dosage form refers to the **package or container** of which the drug has taken **the shape**
- the ability to **release the active ingredient over an extended period**

Classification according to the physical properties

- **Gaseous** dosage forms
- **Liquid** dosage forms
- **Semisolid** dosage forms
- **Solid** dosage forms

I. GASEOUS DOSAGE FORMS

- medicinal gases, inhalation/volatile anesthetics
- aero-dispersions of solid particles or liquid particles

SPRAYS - are composed of various bases such as alcohol or water in a pump-type dispenser

INHALANTS AND AEROSOLS - variety of forms; devices – nebulizers and humidifiers

II. LIQUID DOSAGE FORMS

SOLUTIONS/DROPS

- one homogenous phase
- prepared by dissolving one or more solutes in a solvent or composed of various solutions
- aqueous, oils
- can be administered by all routes

SYRUPS

- sugar-based aqueous solutions that have medications dissolved in them
- with/without flavoring agents
- improve the taste of the drug

ELIXIRS

- sweetened solutions containing dissolved medication in either an alcohol base or water and alcohol base
- alcohol usually covers up the bad taste of the drug
- avoided when used for children

TINCTURES

- alcoholic or hydroalcoholic sol. - herbal extract

EMULSIONS (o/w or w/o)

- a dispersion system consisting of two immiscible liquids used with an emulsifier binds the two together

SUSPENSIONS

- a dispersion system where solid particles are dispersed in liquid phase
- not intended for systemic administration of drugs with high potency
- “shake well” sticker

ENEMAS
- might be administered for retention or evacuation
- to deliver medication to the body, bypassing the stomach while being absorbed
- to evacuate the lower intestine to prepare for surgeries or for women in labor

EYE LIQUID DOSAGE FORMS – DROPS
- smaller volumes, 10-20 ml
- manufactured or compounded
- sterile
- often deserves to employ antimicrobial agent
- isotonic with tears
- vehicle – sterile water (oil)

EAR LIQUID DOSAGE FORMS – DROPS
- usually isotonic
- non-irritating
- vehicle – isotonic aqueous solutions/oils
- not necessarily sterile
- for clearing up infections or cleaning out ear wax buildup

NASAL LIQUID DOSAGE FORMS – DROPS, SPRAYS
- used to treat colds and allergies
- work on the specific site rather than the whole body

PARENTERAL DOSAGE FORMS
INJECTABLES
- for administration using a hypodermic (hollow pointed) needle
- formulated as liquids or powders/lyophilisate for preparation of the solution

INJECTIONS (available as ampoules, vials)
- solutions, emulsions or suspensions
- **sterile, pyrogen-free, isotonic**

INFUSIONS (available in plastic bags)
- I.v. and s.c. route (the demands are as above)
- higher volumes over much larger times (from min to days)
- infusion pump, tubing and flexible canule is needed

I.V. INJECTIONS
- particle-free
- isoacidity is desirable (but different pH often needed to assure solubility of API or chemical stability)
- moderately irritating compounds can be administered
- vehicle – sterile water for injections, co-solvents may be added
- slow administration to avoid problems with „concentration wave“

I.M. and S.C.
- isoacidity should be guaranteed
- API and excipients should be non-irritating
- suspension/emulsion injectables can be administered (depot forms), oil-based vehicles may be used
- the volume administered depends on site of administration

III. SEMISOLID DOSAGE FORMS

UNSHAPED
- **GELS -** systems in which a liquid phase is constrained within a 3D cross-linked matrix
- **CREAMS** - semisolid emulsion systems (o/w, w/o) containing more than 10% of water
- **OINTMENTS -** semisolid systems with the oleaginous , water-soluble or emulsifying base
- **PASTES** - semisolid dispersion system, where a solid particles (> 25%) are dispersed in ointments
- **EYE SEMISOLID DRUG FORMULATION - GELS, CREAMS, OINTMENTS -** sterile and clear,

SHAPED

SUPPOSITORIES ***(for rectal administration***)
- solid dosage form under room temperature
- melting at body temperature
- suppository basis - oleaginous (cacao butter, adeps neutralis) or aqueous (PEGs, glycerinated gelatin)
- different size – children and adult supp.
- different shape – mostly torpedo-like
- both manufactured and compounded

PESSARIES ***(vaginal suppositories)***
- PEGs or glycerinated gelatin base
- mainly to treat vaginal infections

IV. SOLID DOSAGE FORMS

UNSHAPED - POWDERS for external/internal use

SHAPED
- **Tablets, Capsules, Implantates, Transdermal patches and others**

Solid dosage forms
- solid agents can be contained in various packages
- administered by almost all routes except parenterally (IV)
- contain inert ingredients (fillers, binders, disintegrants…)

POWDERS

- for external/internal use
- can be packaged in some forms that allow them to be sprayed, similar to liquid dosage forms

TABLETS = compressed product (API+ excipients – e.g., fillers, desintegrants)

- **Conventional** (can be divided – half/quarters)
- **Coated** (usually not to be divided)
- **Effervescent tablets** (the final dosage form is a solution) – rapid absorption (rapid onset of action)
- **Sublingual tablets** (SL)
- **Chewable tablets** (if swallowing difficulty, children)
- **Vaginal tablets**

LOZENGES/TROCHES

- other forms of tablets that are not meant to be swallowed but to dissolve in the mouth
- release the medication more slowly
- similar to hard candy
- flat, larger than normal-sized tablets
- chalky consistency

CAPSULES

- substances enclosed in the hard/soft water soluble container made of gelatin

➢ **hard**

- consist of cap and body
- filled with powders, pellets, granules
- can be pulled apart to sprinkle the medication onto food

➢ **soft**

- one-piece
- filled with paste, oil
- can be squeezed to dissolve medication in liquid

SOLID DOSAGE FORMS

- **conventional (unmodified) release**
- **controlled release**
- **targeted distribution drug delivery systems**

Conventional release dosage forms

- spontaneous disintegration of the dosage form and dissolution of active ingredient
- drug absorption and distribution is based only on physico-chemical properties of ingredients

Controlled release dosage forms

- the release of active ingredients is under control of the drug delivery system (temporal control)
- avoidance of fluctuations of plasma drug concentration
- decreased frequency of drug administration
- more economical

Controlled release dosage forms

- **Sustained release (SR)** – release of the initial dose and further prolonged release
- **Controlled release (CR)** – properly controlled (0. order) release of active ingredient
- **Pulsatile release**

Controlled release dosage forms

- **Reservoir type –** core consisting of API and excipients is encapsulated by membrane/envelope determining the rate of release
- **Matrix type -** drug is dispersed within the polymer (matrix can be biodegradable – drug is released continuously; can form pore – drug diffuses gradually)

Targeted drug delivery

- PK of the drug is not primarily determined by the physico-chemical properties of the substance
- targeted distribution of the drug
- improved selectivity of action
- overcome unfavorable PK properties (rapid metabolic biotransformation or elimination)
- improved efficacy
- improved tolerability/decreased toxicity

TRANSDERMAL DRUG DELIVERY SYTEMS (TDDS)

- transdermal patches designed for affixing on healthily and clean skin
- controlled drug delivery into the systemic circulation over time

- **Reservoir**/**membrane** systems
- **Matrix** systems
- New „**micro-invasive**“ systems – microneedle arrays

IMPLANTS – parenteral route dosage form

- controlled drug delivery for over a long time (months/years)
- reservoir systems (osmotic/diffusion)
- matrix systems (non-biodegradable, biodegradable polymeric materials with dispersed drug)
- overcomes problems with individual compliance
- mini-surgery is needed
- uneasy to simply discontinue the therapy
- local reactions

EYE SOLID DRUG FORMULATIONS - EYE INSERTS

- soluble, insoluble, biodegradable
- slow release of API

PHARMACEUTICAL DOSAGE FORMS

- **for systemic administration**
  - p.o.
  - s.l. and buc.
  - rectal
  - parenteral
  - transdermal
  - inhalation
- **for local administration** (on the skin or mucosa) - into/onto:
- the eye, nose, ear
- the oral cavity
- the vagina, rectum
- the bronchi
- the skin

ORAL ROUTE (P.O.)

- by mouth
- very convenient
- do not need to be measured
- less expensive
- systemic
- safe
- do not work as quickly as parenterals (IV's)
- some drugs cannot be taken orally because they are not as effective

SUBLINGUAL AND BUCCAL ROUTE

- buccal agents are placed between the gum and cheek
- sublingual agents are placed under the tongue
- the medication penetrates the mouth lining and then enters the bloodstream
- tablets, spray

VAGINAL ROUTE

- **for local drug administration**
- application devices
- **Tablets** – disintegrating in vagina; may also form foam
- **Capsules**
- **Pessars** – vaginal suppositories – hydrophilic bases; both manufactured and compounded
- **Foams, Creams**

RECTAL ROUTE

- rectal dosage forms (suppositories, gels, creams, enemas) for **local and systemic** drug administration
- it can bypass the liver - there may be no first pass effect
- when patient cannot swallow the drug; useful for children
- uncomfortable (poor compliance)
- actual amount of drug absorbed is hard to predict
- local irritation of rectal mucosa

TOPICAL ROUTE

- effects range from localized to
- easy application
- might cause a reaction
- dosing is difficult

Topical dosage forms:

- Aerodispersion – sprays
- Aqueous dosage forms – lotions, medicated shampoo, foam
- Semisolid dosage forms – gels, creams, ointments
- Solid dosage forms – dusting powder

TRANSDERMAL ROUTE

Transdermal drug delivery systems (TDDS)

- pain and stress-free
- easily administered – no need for trained specialist
- long-term drug delivery with minimal fluctuations of drug concentrations
- good compliance
- delivery of the drug can be immediately discontinued
- eliminate a possible upset

PARENTERAL ROUTE

Intravenous (IV), Intramuscular (IM), Subcutaneous (SC)

- parenteral comes from the Greek and means "side of intestine" or "outside of intestine"
- very-small–gauge needles are used
- the length depends on the site being injected
- **it can be a approach of choice in the case of:**
  - problems with oral absorption
  - problems with stability of API in GIT (
  - uncooperative patients
  - urgent need for rapid onset of action
- **limited use due to:**
  - non-compliance (phobias, children)
  - higher risk of adverse reactions, accidental extravasations of some drugs – tissue inflammation, necrosis
  - need for trained personnel; aseptic procedures
  - more expensive
  - once a drug is injected, there is little time to alter its course

LOCAL DRUG ADMINISTRATION INTO THE EYE

- high local concentration
- lower systemic adverse reactions
- minor effects on vision – liquid dosage forms
- API exposure is longer – semisolid dosage forms
- slow release of API – eye inserts
- if not kept sterile during use, can introduce bacteria into the area being treated
- do not last as long as other treatments
- dosage accuracy
- local hypersensitivity