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*Module: Pharmaceutical  
Processes  
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## Chapter 3: Pre-formulation

### 01/ Routes of administration

There are several routes of drug administration, all of which have advantages and disadvantages.

When a general effect is sought, the drug is administered orally or parenteral. If we want to obtain a local effect, we use special preparations such as eye drops, ointments...

Absorption is the process by which any substance brought from the exterior enters the blood or lymph:

- It is direct when the drug penetrates directly into the body (routes intravenous, intramuscular, subcutaneous, etc.);
- It is indirect when the drug must cross a barrier before passing into the general circulation (oral route, application to the skin).

#### 01-01/ Oral (buccal) route (per os)

This is the most used route (70 to 80% of medications). After oral administration, the drug crosses the intestinal barrier then the liver before reaching the general circulation and hence the organs for its therapeutic action.

✓ Advantages	X Disadvantages
• Administration of drugs by this route is easy.	• Drugs travel through the portal vein and pass through the liver where they can be broken down by various enzymes or excreted through the bile.
• It is well accepted by the patient.	• There is irritation of the digestive tract by certain medications (anti-inflammatories, corticosteroids, etc.). The oral route should therefore be avoided in the event of peptic ulcer or gastritis.
• High doses can be taken at one time.	• The action only appears after a latency period corresponding to the absorption time (absorption is faster on an empty stomach).
	• Sometimes absorption is incomplete, or even zero (certain sulfonamides, metal salts).
	• The smell and taste of medicines are sometimes unpleasant (hence the use of flavorings).
	• It cannot be used for drugs destroyed by the digestive tract (peptide hormones such as insulin).
	• The oral route is difficult to use in case of nausea and vomiting.
	• It cannot be used in an unconscious patient...

#### 01-02/ Parenteral or injectable route

This is the most direct route, because it puts the medication directly in contact with the blood or interstitial fluids and avoids the digestive tract. Medications administered by parenteral are liquid injectable preparations (solutions, emulsions, suspensions) or solid (the implants).

✓ Advantages	X Disadvantages
<ul style="list-style-type: none"> <li>• Rapid effect, especially after intravenous administration.</li> </ul>	<ul style="list-style-type: none"> <li>• The injection is sometimes painful,</li> </ul>
<ul style="list-style-type: none"> <li>• Immediate passage into the body.</li> </ul>	<ul style="list-style-type: none"> <li>• It can cause a risk of infection,</li> </ul>
<ul style="list-style-type: none"> <li>• No destruction by the enzymes of the digestive tract, which it helps to avoid.</li> </ul>	<ul style="list-style-type: none"> <li>• There are difficulties with repeated injections because the number of injection points is limited.</li> </ul>
<ul style="list-style-type: none"> <li>• Injection possible at the desired location (for example intracardiac injection).</li> </ul>	<ul style="list-style-type: none"> <li>• Injectable suspensions can only be administered intramuscularly.</li> </ul>
<ul style="list-style-type: none"> <li>• Useful for a patient who is unconscious or unable to swallow.</li> </ul>	<ul style="list-style-type: none"> <li>• You should not inject irritating products, which could damage the vein.</li> </ul>
	<ul style="list-style-type: none"> <li>• The duration of drug action is generally short, especially after administration intravenously.</li> </ul>
	<ul style="list-style-type: none"> <li>• Drugs administered parenterally must be sterile and nonpyrogenic...</li> </ul>

The following table summarizes the different modes of parenteral penetration:

<i>Mode</i>	<i>Abbreviation</i>	<i>Injection site</i>
Intravenous route	IV	Vein in the elbow, hand, wrist
Intramuscular route	IM	Gluteal muscle
Intra-arterial	IA	Femoral artery
Intra-cardiac	IC	Heart muscle
Sub-cutaneous	SC	Under the skin in the connective tissue
Intradermal	ID	Under the skin, at the boundary of the epidermis and dermis

### a) Intravenous route (IV)

This is the emergency route because there is direct penetration into the blood, which allows almost immediate effects to be obtained (around 15 seconds).

The injection is done by syringe or by infusion when the volumes are large. The dosage is precise and controllable because the injection can be stopped at any time if the patient reacts badly. This route can administer only aqueous solutions or emulsions.

Intravenous injection is indicated when a drug is not tolerated subcutaneously or intramuscularly, when it is not absorbed through the digestive tract, and finally in emergency treatments (when action

must be taken quickly). The most common injection site is the vein in the elbow, back of the hand or wrist.

### b) Intramuscular route (IM)

Intramuscular injection (in the upper outer quadrant of the buttock) allows painful preparations to be injected subcutaneously, in particular oily solutions and suspensions. A long bevel needle is used. The speed of resorption of drugs administered intra-muscularly and subcutaneously is very similar.

### c) Sub-cutaneous route (SC)

By this route, drugs are mainly administered in isotonic aqueous solution in administration under the skin, into the connective tissue (belly, shoulder, thigh), with a short bevel needle. This route is used to achieve slow action of the drug. In particular, insulin, adrenaline, low molecular weight heparin and calcium, and vaccines are administered subcutaneously.

⇒ There are other very important routes of administration such as the intraspinal route, which is used whenever it is necessary to obtain local action (meningitis). It is also used during spinal anesthesia. This route allows anesthesia to be carried out in the region of the small pelvis and lower limbs.

### 01-03/ Transmucosal route

#### a) Perlingual route:

It corresponds to the lingual mucosa and the mucous membranes of the lower part of the mouth, the mouth, and the inner side of the cheeks. Small tablets that are placed under the tongue, aqueous or alcoholic solutions, and granules (homeopathy) are administered this way. It is an easy, practical and rapid route of administration allowing direct penetration of the drug into the general circulation, without passing through the liver, which avoids the first pass hepatic effect. Only drugs with powerful pharmacological effects can be used by this route (adrenaline, estrogens, androgens, etc.). For example, it is an emergency option in the treatment of angina attacks.

#### b) Rectal route

As the rectal mucosa is very vascularized, it makes it possible to obtain a general or local action depending on the type of medication. Suppositories, enemas and rectal ointments are administered this way. Suppositories are used to obtain a local effect (hemorrhoids, proctitis, constipation) or a general action.

✓ Advantages	X Disadvantages
<ul style="list-style-type: none"> <li>The drug is neither affected by the action of digestive enzymes nor that of gastric hydrochloric acid.</li> </ul>	<ul style="list-style-type: none"> <li>It can cause irritation or even ulceration of the rectal mucosa.</li> </ul>
<ul style="list-style-type: none"> <li>This route is convenient in children and infants, in patients who are nauseous, unconscious or unable to swallow.</li> </ul>	<ul style="list-style-type: none"> <li>It may be considered unpleasant by the patient.</li> </ul>

	<ul style="list-style-type: none"> <li>• It does not allow the hepatic barrier to be avoided because resorption takes place via the superior hemorrhoidal veins which lead to the portal vein and therefore to the liver (first-pass hepatic effect).</li> </ul>
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### c) Vaginal route

The drugs used by this route are intended for local action because the vaginal mucosa is poorly permeable. Eggs, vaginal tablets, creams and vaginal capsules are used for antibacterial, antiseptic, antiparasitic and antifungal treatments, as well as for hormonal indications.

### d) Nasal route

It is used to locally treat conditions of the nasal area (powders, ointments, solutions).

### e) Ocular route

The fragility and sensitivity of the ocular mucosa require the use of perfectly controlled and sterile medications (eye drops and ophthalmic ointments).

### 01-04/ Pulmonary route

The pulmonary tree, which has a surface area of 100 m<sup>2</sup> in adult humans and significant vascularization, allows rapid absorption of drugs.

This pathway is used to absorb gases (oxygen, chloroform, ether, etc.). A large number of medications (sulphonamides, antibiotics, anti-asthmatics, etc.) can be administered using aerosols, which are mist of fine medicinal particles.

### 01-05/ Cutaneous and percutaneous routes

It involves the direct application of a medication to the skin by different means. The action is local if the components cannot penetrate through the skin. It is general if the components can cross the skin barrier.

Only healthy skin is an effective barrier between interior and exterior environments. Otherwise (lesions, burns, eczema), any medication applied to the skin will be significantly reabsorbed.

Forms of percutaneous administration are ointments, gels, lotions, patches, etc.

The main disadvantage of the cutaneous route is a hypersensitivity reaction when using patches, due to the adhesive.

### 01-06/ Criteria for choosing a route of administration

- Depending on the type of action desired: local or systemic.
- Depending on the desired action time: crisis treatment (emergency) or basic treatment (daily).
- Depending on the volume to be administered: large (>20ml), less large (5-20ml).
- Age-related factors: adult, child, old
- Factors linked to the administered substance: interaction with physiological constituents.

### 02/ Galenic forms

The medicine can take different forms; the latter are called “*Galenic forms*”.

#### a) Capsules (type I)

The capsule is made up of two nested, hollow, cylindrical-spherical capsules made up of gelatin. The active ingredient and excipients, in powder form, are contained inside the container.

There are several sizes of capsules which vary from size 0 (very large) to size 3 (very small). The presence of dyes (iron salts, titanium oxide) makes it possible to differentiate them. In the stomach, the capsule dissolves and releases the active ingredient.

#### b) Capsules (Type II)

The capsules are soft in consistency, and are most often intended to contain a liquid (such as vitamins) sealed in an airtight manner.

#### c) Pills

The pill is a spherical mass ( $\varnothing = 5-10$  mm) made up of active ingredients associated with gum arabic and simple syrup as binders. These pharmaceutical forms are increasingly little used anymore.

#### d) Tablets

Are hard, discoid or ovoid masses obtained by compression of a mixture of powders consisting of active ingredient(s) and excipients. These latter can be coated with a thin film (film-coated or coated tablet).

**NB: The scored tablet can be cut in half or in quarters. Coated tablets or extended release can never be cut or chewed.**

#### e) Liquid oral forms

Syrup: It is a viscous liquid made from simple syrup. The simple syrup consists of 1.8 kg of sucrose dissolved in 1 liter of water.

Suspension: This is the result of the dispersion of a solid in a liquid phase.

Emulsion: It is the result of the dispersion of a liquid phase in another immiscible phase.

#### f) Dermatological forms

Ointment: Medicine for external use of an ordinarily soft consistency, having as base of fatty substances (lanolin, vaseline, oil, etc.) in which the principles are incorporated active ingredients in the form of powder, resin, essential oil, etc.

Cream: Medicine for external use of an ordinarily soft consistency, having as base of fatty substances (oil) emulsified in an aqueous phase (oil in water), or vice versa (water in oil). The active ingredients are dissolved or dispersed in these phases.

Gel: Medicine for external use of an ordinarily soft consistency, having as a base an aqueous phase. It is a non-greasy preparation. The gel may be translucent. The active principle is dispersed or solubilized in this phase.

Lotion: Liquid medication for external use intended to be applied to the skin or hair.

Shampoo: Liquid medicine for external use intended to be applied to the hair, before being eliminated by rinsing. (e.g. treatment of pediculosis, baldness, etc.).

#### g) The suppository

It is a medicine for rectal use with a solid consistency and an ovoid shape or conical (1 to 3 g). It is made up either of a mixture of glycerin and gelatin, or of a mass oily. The active ingredient is dissolved or dispersed in the molten suppository mass, which is then poured into a mold. The active ingredient is resorbed and distributed throughout the body.

#### h) Eggs:

It is a medication for vaginal use of soft (glycerin) or solid consistency (fat mass), olive-shaped. The active principle has an essentially local action (antibiotic, antifungal, etc.).

#### i) Drops

Eye drops: Liquid medicine intended to be administered in the form of drops in the eye.

Nasal drop: Medicine in the form of a drop, liquid spray, powder spray administer nasally. The action is either local (e.g.: decongestant, disinfectant), or systemic (hormones....)

Ear drop: Liquid medication to be administered into the ears.

### 02-01/ Criteria for choosing a route of administration

Galenic forms can be classified according to two criteria: consistency (solid, liquid and semi-solid) or according to the route of administration.

#### 02-01-01/ Classification of pharmaceutical or galenic forms according to their consistency

##### a) Solid dosage forms

Powder, granule, powder sachet, cachet, hard capsule (capsule), soft capsule, tablet (naked, coated, effervescent, dispersible, multilayer, matrix, osmotic), oral lyophilisate = lyoc®, officinal paste, lozenge, tablet, pill, spheroids, suppository, implants, adhesive forms skin and transdermal device...

##### b) Semi-solid dosage forms

Mousse, ointment, cream, gel, paste...

##### c) Liquid dosage forms

Solution, syrup, suspension, emulsion, mouthwash, gargle, lotion...

### 02-01-02/ Classification of pharmaceutical or galenic forms according to the route of administration

#### a) Forms for the oral route

Powder, granule, sachet of powder, sachet of granules, cachet (obsolete form), hard capsule, soft capsule, tablet: naked, coated, effervescent, dispersible, multilayer, matrix, osmotic, adhesive, oral



lyophilisate = lyoc®, pill, spheroids, solution, syrup, elixir, potion, suspension, emulsion, mouthwash, gargle, herbal teas, ampoules of oral solution sachet of suspension or gel...

#### b) Forms for the cutaneous route

Local action, systemic action, lotion, solution, foam, aerosol, powder (antiseptic, talc), sinapisms (poultice), ointments (monophasic excipient), cream (biphasic excipient), gel (liquid with agent gelling agent), paste (excipient in suspension with powder at more than 40%)...

#### c) Ophthalmic forms (ocular route)

Local action Eye drops, eye ointment, eye wash solution, lens preparations contact...

#### d) Forms for the rectal route

Local action, systemic action, Suppository, solution, rectal dispersion, rectal ointment and rectal foam.

#### e) Injectable forms (parenteral route)

Local action, systemic action Route of emergency treatment, resuscitation Injectable preparations (small volume, syringe + needle), injectable preparations for infusion (large volume, bottle or bag + catheter + needle), powders for preparations injectable (presented with solvent for extemporaneous solution or suspension)...

#### f) Forms for the nasal route

Local action, systemic action, drops, aerosols...

#### g) Forms for the vaginal route

Local action, systemic action, Eggs, vaginal tablets, ointments, foams and solutions...

#### h) Forms for the auricular route

Local action Eardrops, ear ointments....

### 03/ Biopharmaceutical classification

The biopharmaceutical classification system (BCS) is a system to differentiate drugs on the basis of their solubility and permeability. This system restricts the prediction using the parameters of solubility and intestinal permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important because 85% of the most sold drugs in the United States and Europe are orally administered.

#### 03-01/ BCS classification

According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability.

- Class I - high permeability, high solubility
  - Example: metoprolol, paracetamol<sup>[2]</sup>
  - Those compounds are well absorbed and their absorption rate is usually higher than excretion.
- Class II - high permeability, low solubility
  - Example: glibenclamide, bicalutamide, ezetimibe, aceclofenac

- The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.
- Class III - low permeability, high solubility
  - Example: cimetidine
  - The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
- Class IV - low permeability, low solubility
  - Example: Bifonazole
  - Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

#### 04/ Dissociation coefficient, partition coefficient

Drug distribution refers to the passage of drug from blood to tissues, or from tissues to blood and the drug levels in different tissues.

After entering the bloodstream (see Drug Absorption), the drug circulates quickly throughout the body; the average time for blood circulation is one minute. As the blood circulates, the medication moves from the blood compartment to the body's tissues.

Once absorbed, most drugs are not distributed evenly throughout the body.

-Water-soluble medications (water-soluble medications), such as the antihypertensive drug atenolol, tend to stay inside the blood flow and fluid surrounding cells (interstitial space).

-Fat-soluble drugs (fat-soluble drugs), such as the anxiolytic clorazepate, tend to concentrate in fatty tissues.

-Other medications concentrate primarily in a small region of the body (e.g., iodine products are found primarily in the thyroid gland), because certain tissues have a particular ability to attract and retain a particular type of medication (affinity).

Products penetrate different tissues at different rates depending on their ability to cross membranes. For example, the antibiotic rifampicin, a highly fat-soluble drug, quickly penetrates the brain while the antibiotic penicillin, a hydrophilic drug, does not. Usually, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs. For certain drugs, specific transport mechanisms facilitate their entry or exit from tissues. Because they bind strongly to proteins circulating in the blood, some drugs leave the bloodstream only very slowly. Others, less firmly bound to plasma proteins, leave it quickly to enter the tissues.

Virtually all drug molecules passed into the blood can be bound to plasma proteins. The protein-bound fraction of the drug is generally inactive. When the unbound drug is distributed into the tissues and its proportion in the blood decreases, the plasma proteins gradually release the fraction of product bound to them. Thus, the drug retained in the blood compartment can act as a reservoir.

Some drugs accumulate in certain tissues (e.g., digoxin accumulates in cardiac and skeletal muscles), which can then serve as reservoirs for additional drug. These slowly release the drug into the bloodstream, preventing its presence in the blood from dropping quickly. Some medications, such as those stored in fatty tissue, leave the tissue so slowly that they remain in the bloodstream for several days after treatment stops.

The distribution of a medication can also vary from person to person. For example, obese people are likely to store larger amounts of lipophilic drugs than lean people, who can only store a relatively small amount. Older people, even those who are lean, can accumulate large amounts of lipophilic drugs as body fat increases with age.

### 05/ Regulating Active Pharmaceutical Ingredients

The safety and effectiveness of drug products are directly impacted by the caliber of its active components and are ensured through process optimization. In numerous cases over the past few decades, subpar API Process Development and production as well as tainted active components have been linked to adverse health effects, including death. Because of this, regulatory procedures and approvals of active ingredients have been made more stringent in most of the countries across the globe.

The regulation of active components will strengthen the pharmaceutical drug supply chain, improve the quality and safety of medications for patients, and align a company with global regulatory practices.

Active pharmaceutical ingredients (APIs) are prequalified by an independent process that determines those that are high-quality and produced in accordance with WHO Good Manufacturing Practices (GMP). Prequalification of a Finished Pharmaceutical Product (FPP) for which prequalification is sought is significantly easier if an API that has already received prequalification is employed in its production.

### 06/ Pharmaceutical Industry in Algeria: cooperation with USA

After years of restricted market access and uncertainty for American pharmaceutical companies, 2021 is finally a year of positive change. Last year, the Algerian Government established the Ministry of Pharmaceutical Industry (MOPI) and the National Agency for Pharmaceutical Products (ANPP) to help modernize Algeria's pharmaceutical industry. Since their inception, both organizations have made significant progress in several critical areas identified by industry, including drug pricing procedures, overly burdensome regulations, and a dysfunctional process for establishing and maintaining marketing operations.

American pharmaceutical exporters should take note of the following market developments when considering entering or expanding in Algeria:

⇒ In December 2020, MOPI issued new regulations to decrease the wait times for registering new drugs dramatically. What used to take up to five years could now take as little as five months for proprietary drugs (four months for technical analysis and one month for pricing) and as little as three months for generic medicines.

⇒ At the end of February 2021, MOPI issued regulations that resolved the longstanding issue of representative offices for foreign pharmaceutical companies operating in Algeria. The new regulation permits foreign pharmaceutical companies to market their products locally and establishes clear rules for establishing local pharmaceutical entities. MOPI also allowed for temporary authorizations of up to one year for medicines prescribed to treat serious diseases when there is no equal treatment in the market and when approved by another regulatory body (such as the U.S. Food and Drug Administration).

These positive changes demonstrate MOPI's desire to improve Algeria's pharmaceutical industry, and the Commercial Service in Algeria will monitor how these changes impact U.S pharmaceutical companies during the rest of 2021.