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PHARMACOLOGY (ROUTE OF DRUG ADMINISTRATION)

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ABSTRACT :-

The route of administration is the way through which the dosage form is administered into the body for treatment of various diseases and disorders. Various routes of administrations play a marked role in the bioavailability of the active drug in the body. In present review these routes are included with their advantages and limitations. This is an attempt for the initials of field to familiarize with the routes of administrations with their significances.

Systemic absorption of a drug depends on its physicochemical properties, the nature of the dosage form on which it is included and the anatomical and physiological characteristics of the site of absorption.

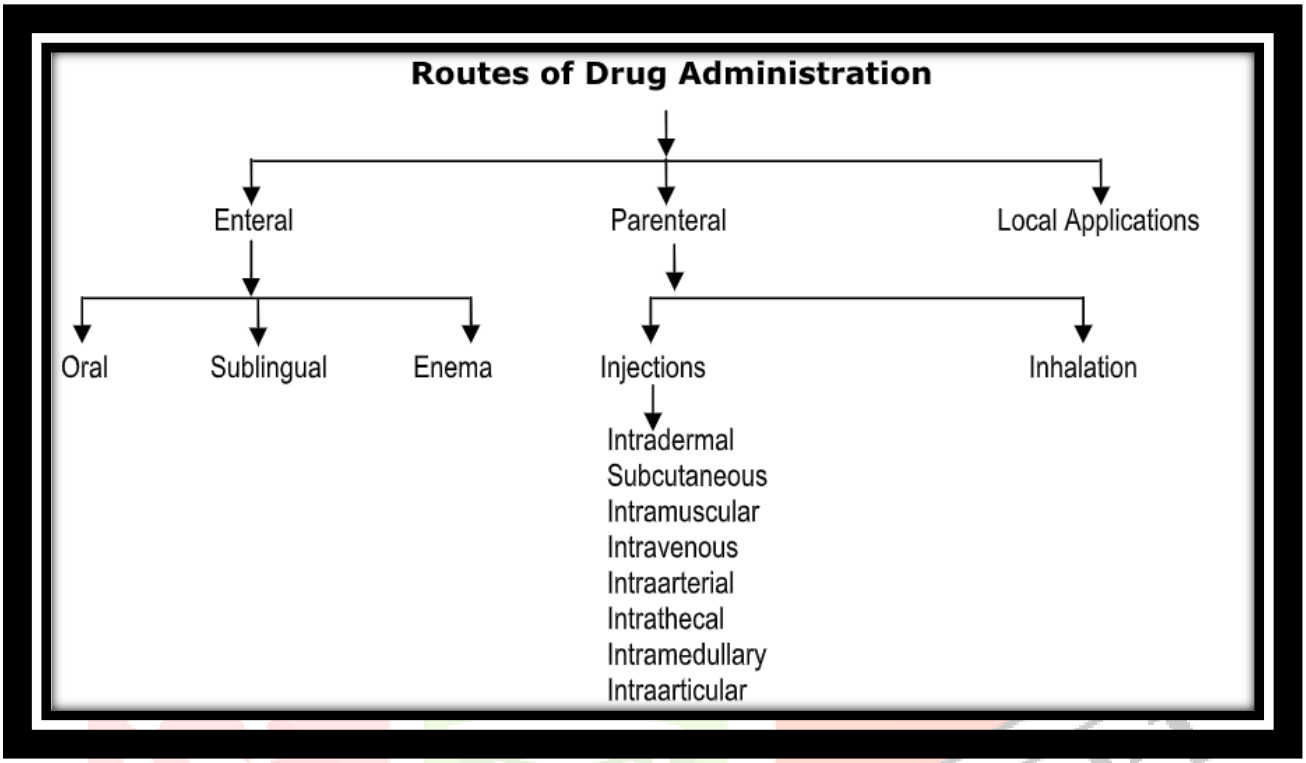
Keywords :- Absorption; bioavailability; biopharmacy; dosage forms; enteral route; intravenous route; intramuscular route; nasal route; oral route; parenteral route; pharmaceutical products;

Introduction :- The route of administration of a medication directly affects the drug bioavailability, which determines both the start and the duration of the pharmacological effect. Some considerations must be taken into account when designing a drug dosage form: (1) the intended route of administration; (2) the amount or dose to be administered; (3) the anatomical and physiological characteristics of the site of absorption, such as membrane permeability and blood flow; (4) the physicochemical properties of the site, such as pH and osmotic pressure of physiological fluids; and (5) the potential effect of the medication over the site of administration. When the systemic absorption of a drug is desired, medications are usually administered by two main routes: the parental route (through skin by injection, avoiding the digestive system) and the enteral route (directly at some point of the gastrointestinal tract). To a lesser extent, the pulmonary (or respiratory) and nasal routes are employed. Other routes of administration, such as ophthalmic and vaginal, are not included here because their application is almost exclusive for local (not systemic) drug administration.

It becomes more than important to know the numerous principles and modes of drug administration, as they are clinically pertinent in therapeutics, and help in evading any possible injury to patients getting these drugs. Although there are numerous principles of drug administration, the five significant ones are as follows: the right patient, the right drug, the right dose, the right time, and the right route of administration. Modes or routes of drug administration differ from the extensively administered oral route to parenteral and inhalational routes. There are also some specialized routes and modes of drug delivery, for example, the liposomal delivery, prodrug delivery, and others. Each of these routes of administration has its own advantages and disadvantages, which must be considered and compared to each other before selecting the same. This chapter deals with the key principles and routes or modes of drug administration. Factors determining route of administration are as follows: 1. Drug characteristics like

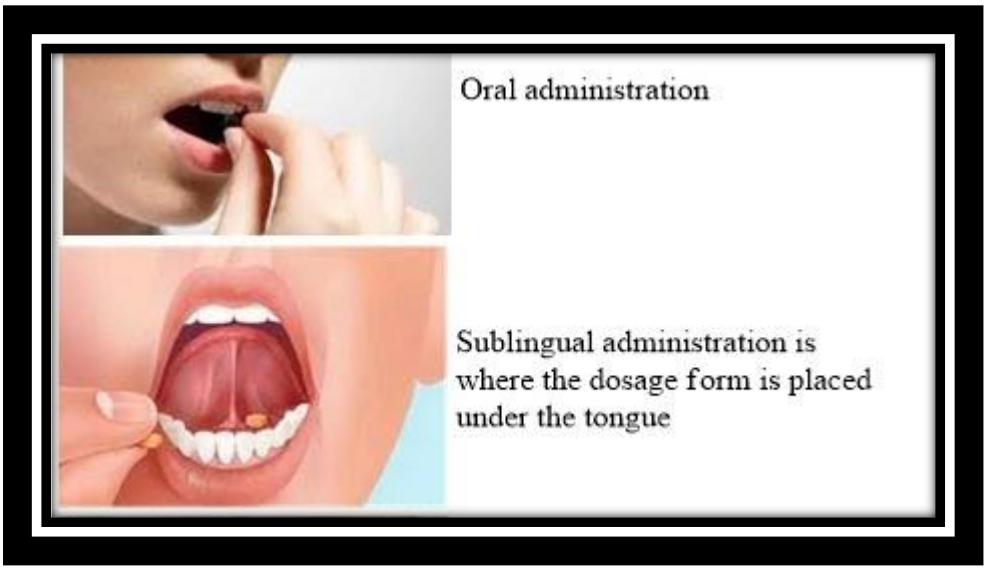
state of drug (solid/liquid/gas), and other properties of drug such as its solubility, stability, pH, and irritancy. 2. Clinical scenarios such as emergency or regular treatment. 3. Patient conditions like unconscious state, or if patient is experiencing diarrhea or vomiting. 4. Age. 5. Comorbid diseases.

6. Patient/doctor choice. 7. Rate and extent of absorption of the drug from different routes. 8. Effect of digestive enzymes and first-pass metabolism on the drug. Routes of drug administration can be divided broadly into two categories: local and systemic (Fig. 2.1). Systemic route includes enteral route which further comprises oral and rectal (drug is directly administered into the gastrointestinal tract [GIT]), whereas parenteral route comprises sublingual (under the tongue), inhalation (into bronchi) and injection. Further, injection includes intravenous (IV, into the vein), intramuscular (IM, into the muscle), and subcutaneous (SC, under the skin).



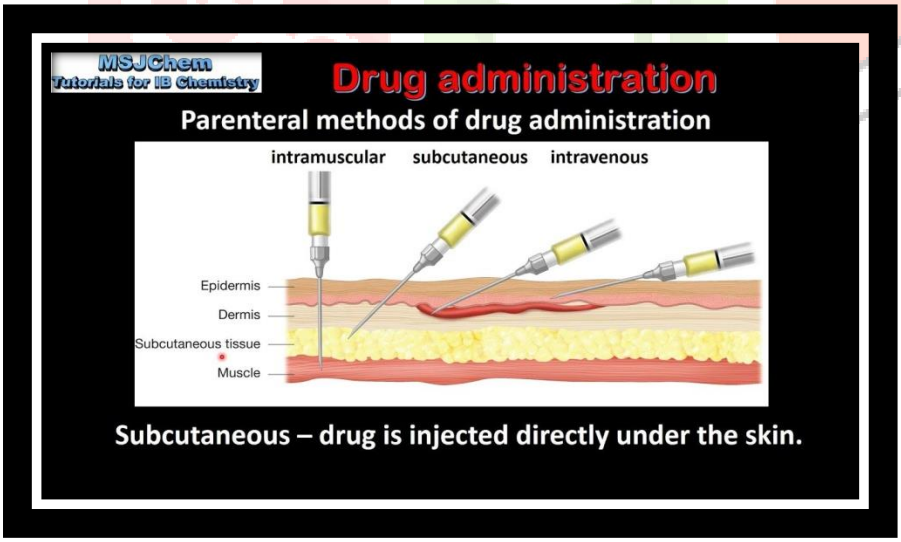
Local Route :-

It is one of the simplest routes of drug administration, wherein the drug can be given at the desired site of action. Systemic absorption of drugs is minimal, hence systemic side effects can be avoided. Following are some of the local routes: Topical The drugs applied to skin/mucous membrane for local actions. A few examples are as follows: • Oral cavity—Drugs can be delivered only to oral mucosa in the form of lozenges or rinse, for example, clotrimazole troche for oral conditions. • GIT—Nonabsorbable drug can be used to have local effect only, for example, neomycin for gut sterilization before surgery. • Rectum and anal canal—Drug in liquid/solid form is used through this route for various actions. ○ Evacuant enema: Through this route, drugs are used for bowel evacuation, for example, soap water enema. Soap acts as lubricant and water stimulates the rectum. ○ Retention enema, for example, methylprednisolone in ulcerative colitis.



Parenteral routes

of administration Parenteral drug administration is carried out directly through the skin, in or towards systemic circulation. It is the route of choice for drugs that cannot be absorbed orallyand/or that are unstable in the gastrointestinal tract (e.g. insulin, heparin). These routes of administration are also used for the treatment of unconscious patients or under circumstances that require a rapid onset of action. Parenteral routes of administration exhibit higher bioavailability than other routes and are not subjected neither to first-pass metabolism nor to the sometimes-extreme conditions of the gastrointestinal environment, while offering the greatest control over the real drug amount that accesses systemic circulation. As main drawbacks, drug administration by these routesis irreversible and can cause fear, pain, tissue damage and/or infections(Florez, 1998). Parenteral administration can be performed by injection (small volumes), infusion (large volumes) or implant, and while its typical goal is to achieve systemic effects, it can also be used locally on a specific organ or tissue by injecting the pharmaceutical active ingredient directly on the site of action, in order to minimize systemic adverse effects (Øie and Benet, 2002). The three main parenteral routes are intravenous (IV), intramuscular (IM) and subcutaneous



Intravenous (IV) :-

Administering a drug through the IV route involves the introduction of a drug solution through a needle, directly into a vein. It is the best way to deliver a dose rapidly and accurately, as the drug enters directly into systemic circulation without the delay associated to absorption processes, achieving its therapeutic effect faster than by any other route. For the same reason, this route presents a bioavailability of 100%, since the pharmaceutical active ingredient usually reaches the site of action without suffering alterations due to presystemic effects. There are three main methods to administer medications by IV route

Fast IV injection :-

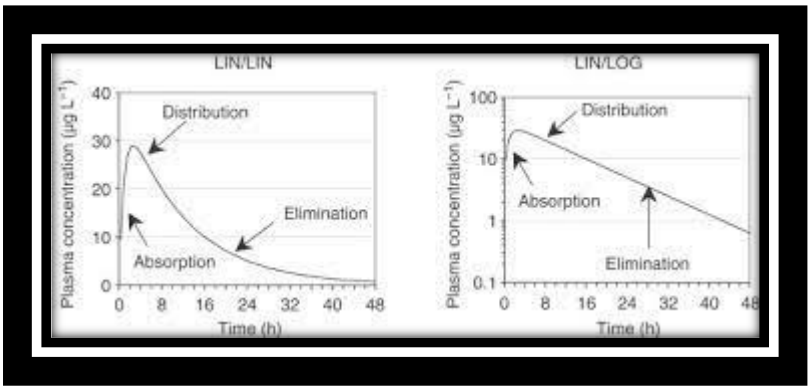
Also called 'IV bolus', is the administration of a single dose by direct injection into a vein, so it only supports small volumes (smaller than 10 ml). After an IV bolus injection, the drug diluted in the venous system reaches the heart, is pumped to the lung and is distributed to the rest of the body by the arterial system. According to the fraction of the arterial blood flow that reaches the site of action, therapeutic effects can be observed even 20 - 40 seconds after injection), and thus this is a very useful route for emergencies and pain management (Saxen, 2016).

Slow IV infusion :-

It consists in the administration of the medication into a vein, during a prolonged period of time (large solution volumes). The amount of drug administered in a certain period is determined by the rate of infusion, and the medication enters the body by gravity or by an infusion pump, forcing the solution to pass through a plastic catheter inserted in a vein. Although for patient comfort veins of the forearms (basal and middle cephalic veins) or in the wrists (cephalic accessory and medial antebrachial) are the most common sites, IV administration can be performed in any superficial vein. In certain cases, it may be necessary to resort to a central IV route, which consists in a catheter located at the outlet of the superior vena cava (right atrium). This is required when it is not possible to channel peripheral routes, for prolonged treatments or when hypertonic solutions must be administered (Boylan and Nail, 2002)

Pharmacokinetic characteristics of IV administration :-

An example of a typical pharmacokinetic profile (drug plasma concentration vs. time) obtained after an IV bolus is shown in Figure 6.1.A. After the maximum concentration peak, an exponential decay is observed, and the drug concentration rapidly falls to sub-therapeutic levels (that is, below the minimum effective concentration). This is the reason why when 4 longer times of effect are desired, slow IV infusion is used and constant plasma drug levels are achieved (Figure 6.1.B). Additionally, slow infusions do not exhibit significant fluctuations of serum drug concentrations, as indeed occur with repeated IV bolus or IM administrations (Figure 6.1.C) In the case of drugs with long systemic half-life, for which the initiation of the therapeutic effect by IV infusion could be slow, it is common to administer a loading dose by IV injection to rapidly achieve the therapeutic level, after which systemic concentrations are maintained within the therapeutic range by controlling the rate of infusion (Figure 6.1.D). It should be noted that as IV injection allows obtaining high systemic concentrations in a very short time, highly vascularized and perfused organs (such as heart, lungs, liver and kidneys) are also subjected to high concentrations in a short time, which may produce unwanted side effects. For this reason, this type of administration must be done slowly, monitoring for possible signs of intoxication. IV phenytoin solution, for example, must be administered at a speed of less than 50 mg/min, since faster administrations may cause hypotension, cardiovascular collapse or CNS depression (FDA and CDER 2014).



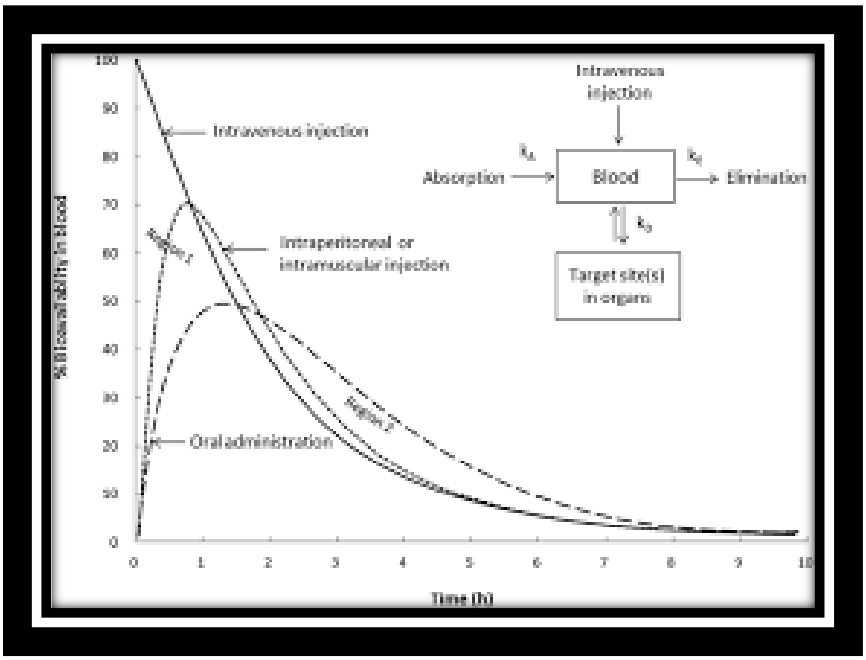
Physicochemical and technological considerations for IV drug administration :-

The IV route of administration is only applicable to aqueous solutions, since suspensions and oily solutions carry the risk of embolism and/or thrombophlebitis. Special care must be taken when selecting the vehicle used to solubilize the drug, since even in the case of aqueous solutions, precipitation of a drug that is poorly soluble could occur during injection, especially in those cases where the drug was solubilized using co-solvents or surfactants. A well formulated parental solution is that which, besides having the required drug dose completely dissolved in the vehicle, allows mixing the drug into circulation, without risk of precipitation. This represents another reason to always perform injections in a slow manner. On the other hand, there are vehicles capable of producing undesired effects in particular populations: phenobarbital, for example, is usually prepared in solutions with variable proportions of propylene glycol (PG), a solvent that can produce hyper osmolarity in children. Additionally, since the metabolic route responsible of metabolizing PG is not completely developed in children under the age of 4, repeated IV injections containing PG could generate toxicity in the paediatric population (Lim et al., 2014). Regarding the formulation pH, it is desirable to formulate medications at physiological-like pH values. If there exist stability and/or solubility reasons not to do so, and a more extreme pH value is needed, the injected volume and the speed of injection should be carefully monitored, since injection may be accompanied by local pain and/or irritation. Injectable phenytoin is formulated at a pH of 10-12 because of the low solubility of the drug at lower pH values. Therefore, precautions should be taken during IV injection of phenytoin to avoid extravasation of the solution and consequent tissue damage, ranging from a simple local irritation to tissue necrosis and ulceration (Douglass, 2018). In the case of solutions that have a higher osmolarity than physiological fluids (anaesthetics, diuretics, parental nutrition, etc.), it is recommended to administer them in large calibre veins or even through a central IV route, to achieve a rapid access to the heart and the consequent dilution of the solution in a larger volume. Prolonged-time infusions as well as the use of highly irritating products may injure the vascular wall and produce venous thrombosis. Consequently, this route is reserved for cases of necessity, and for its use, maximum precautions of asepsis and a rigorous control of the injection technique are imposed.

Intramuscular (IM) :-

It consists on the injection of the medication into the muscle tissue, which can be done in different areas (Boylan and Nail, 2002): 6 • Upper part of the arm: deltoid muscle, admits approximately 2 ml. While it may result painful for the patient, this area generates the higher rate of absorption. • Glutes: dorsogluteal muscle, is the zone that admits higher volumes (7-8 ml approximately) although with lower rate of absorption due to the higher amount of adipose tissue. • External thigh face: vastus lateralis muscle, admits around 5 ml. It is the recommended zone for babies and children, since due to its minor muscle development, gluteal zone carries a high risk of nerve damage. After IM injection, drug must be absorbed to reach the bloodstream, so there is a delay until the beginning of the therapeutic effect. Figure 6.2 comparatively shows plasma concentration profiles vs. time obtained after the administration of a drug through IV, IM an oral route. As previously stated, after an IV injection, the drug reaches maximum plasma concentration almost instantly, so the peak is often not observed, and instead a direct exponential decay is seen.

Physiological factors that modify the IM absorption of drugs After the IM administration of a pharmaceutical product, drug absorption occurs by diffusion from the muscle to the surrounding fluid, and from there to the blood. Different muscular tissues have different blood supply: e.g. the blood flow to the deltoid muscle is higher than the gluteus muscle. Muscle blood flow also increases during exercise or with fever. In contrast, very low blood pressure is accompanied by poor muscle flow and capillary closure, compromising the drug absorption process. The presence of adipose tissue also contributes to slow down the absorption process, so it is common to observe unusual absorption profiles after IM injection to obese patients. The pharmacokinetic behaviour of the IM route may also be altered in neonates and preterm infants, as well as in pregnant women and elderly people.



Technological factors that modify the IM absorption

of drugs By changing the preparation vehicle, IM injections can be formulated to release the drug in a slow or rapid manner. Aqueous solutions are the base of IM immediate release preparations, since the drug is rapidly absorbed from the injection site. An example are lyophilized solids which are dissolved in an aqueous vehicle immediately prior to administration. The onset of the effect usually takes around 30 minutes, and its duration depends on the drug's half-life. In the case of ionisable and poorly soluble compounds, it is always convenient to formulate them in buffer solutions of a pH close to the physiological, otherwise they could precipitate at the injection site. The injectable solution of phenytoin, for example, is usually administered 8 intravenously not only because its formulation pH (close to 12) is extremely irritating to the muscle, but also because the low pH value in muscles and the lack of dilution (in contrast to the IV route) may cause the precipitation of the drug, which is then slowly re-dissolved, generating a slow and erratic absorption process (Fontes Ribeiro, 2005). On the other hand, drugs with very low aqueous solubility must be dissolved in other solvents like PG or mineral oils, whose viscosity delays the drug diffusion to the bloodstream. Additionally, the drug must be partitioned between the carrier and the physiologic aqueous environment for its absorption, which contributes to the relatively slow and sustained release profiles typically obtained with these vehicles. All the aforementioned characteristics have been exploited for the design of prolonged action IM preparations, that allow time intervals of several hours, days or even weeks between doses. Such preparations comprise both in oily solutions (e.g. estradiol, testosterone) and aqueous suspensions forms (e.g. penicillin G procaine, methylprednisolone). Moreover, some drugs, including peptides and proteins, have been formulated as emulsions, suspensions, liposomes and even nanoparticles for IM injection, in order to achieve adequate pharmacokinetic profiles for each active ingredient (Hwang et al., 2016; Xie et al., 2018). In general, hypertonic solutions are contraindicated by this route (as by subcutaneous administration) and should be administered by IV route with the already mentioned precautions.

Subcutaneous (SC) :-

A scheme of the different sites for parenteral drug administration is presented in Figure 6.3. SC administration of drugs consists in injecting them under the skin into the adipose layer beneath the dermis, which is why it has also been called hypodermic administration. It is usually performed on the external side of the arm or thigh, or on the anterior face of the abdomen, and generally admits smaller injection volumes than IM route.

Medications given using a subcutaneous injection :-

Medications administered by subcutaneous injection include drugs that can be given in small volumes (usually less than 1 mL but up to 2 mL is safe). Insulin and some hormones are commonly administered as subcutaneous injections.

Other drugs that need to be given very quickly can also be administered via subcutaneous injection. Epinephrine comes in an automated injector form, called an EpiPen, that's used to quickly treat severe allergic reactions. While it's intended to be given intramuscularly, epinephrine will also work if given subcutaneously.

Some pain medications like morphine and hydromorphone (Dilaudid) can be given this way as well. Drugs that prevent nausea and vomiting like metoclopramide (Reglan) or dexamethasone (DexPak) can also be given via subcutaneous injection.

Formulations for subcutaneous administration :-

As for the IM route, the injected solutions must be neutral or isotonic, otherwise they result irritating and may cause pain and necrosis. Unlike the IM route, though, it is not advisable to inject oily solutions by SC route, as they can become clogged and cause and sterile abscess. One of the most interesting features of this route of administration are the forms of SC depot and continuous SC infusion, by which the drug is released slowly, maintaining stable blood levels for a prolonged time. Among the best-known SC implants are contraceptives devices containing hormones such as levonorgestrel or etonogestrel, which consist in a tiny bar of around 40 mm long and 2 mm wide of a non-biodegradable plastic material that acts as a controlled release membrane. These devices are implanted surgically (prior local anaesthesia) in the inner part of the arm, from where they release the drug throughout a given period (3-5 years depending on the device), after which they must be removed (FDA, 2016). On the other hand, systems for constant SC infusion, such as insulin pumps or morphine infusers, allow small volumes of solution to be introduced at a very slow rate in the subcutaneous tissue. There are several types of insulin pumps but in general they consist in mechanic, small and portable devices electrically controlled (the patient carries them), which contain an insulin reservoir, connected to a cannula inserted subcutaneously, usually in the abdomen. These systems allow insulin release during 3 or 4 days, thus reducing the variability associated to injections. Over the years, more and better

models have been designed, and nowadays there are programmable devices that allow a basal infusion adjustable to the patient schedule (working days, weekends) and insulin bolus on demand, to cover food ingestion (Partridge et al., 2016). Finally, elastomeric infusion systems or infusers are lightweight devices, consisting of a cylindrical plastic container, within which there is a balloon or an elastomeric reservoir. The formulation to be infused is introduced in this balloon causing it to swell. The distended balloon exerts a constant pressure and expels the contents through a tube (at typical speed of 0.5-2 mL/h) connected to a catheter previously implanted in the patient's SC tissue. These systems are mainly used for the administration, both ambulatory and during hospital stays, of analgesic drugs in cancer patients under palliative care or in pain therapy (Lucendo Villarín and Noci Belda, 2004;

Pharmaceutical forms for sublingual and buccal administration :-

Although there are several products on the market for these routes of administration, only a small fraction corresponds to systemic action products, while most are topical (not treated here). Buccal administration products are usually prolonged-release medications, so they are formulated as patches or very adhesive tablets for higher comfort during prolonged contact with the oral mucosa (Montenegro-Nicolini and Morales, 2017). SL tablets, on the other hand, are usually of rapid dissolution so that the active ingredient is rapidly absorbed preventing swallowing losses. In addition, they should be small, without angles or edges, and insipid, in order to not stimulate patients' salivation. Classic examples of drugs administered by this route are the cardioactive nitroglycerin and isosorbide dinitrate, indicated for the treatment of angina pectoris, congestive heart failure, acute myocardial infarction and other peripheral vascular diseases. They are potent drugs capable of achieving their effect (coronary vasodilatation and relief of left ventricular work by reducing venous return) with only a small absorbed drug amount. Administered by buccal or SL route, rapid onset action is achieved, with the additional advantages of: • The effect can be stopped easily, which does not happen when the parenteral route is used. • It avoids the extensive first-pass metabolism that these drugs suffer after oral administration. Figure 6.7 shows the serum levels of nitroglycerin (NTG) obtained after sublingual, oral and transdermal administration (Blumenthal et al., 1977). It is observed that by SL route, the maximum concentration is reached before 10 min. However, the drug elimination rate is also rapid, so this route is only suitable for acute treatment. Chronic treatments are performed orally; despite the fact that relatively high doses are required to compensate the presystemic elimination of the drug

Absorption of drugs by the rectal route :-

The predominant mechanism for the entry of drugs and other xenobiotics at the rectal level is the passive diffusion across epithelial cell membranes, other transport mechanisms not being considered relevant. Due to the reduced surface area and the shorter residence times in comparison to the oral administration, the physicochemical characteristics of the drug and the technological and biopharmaceutical aspects of the formulations are critical factors for the rectal absorption. In general, lipophilic drugs are better absorbed than hydrophilic drugs, the latter usually presenting slow absorption kinetics and incomplete absorption. As mentioned in the previous sections, ionisable molecules reach their maximum absorption rate at pH values that minimize their ionization (Desai, 2007). With regard to the type of pharmaceutical dosage form, the rectal route allows for the administration of solid dosage forms, mainly suppository (emulsion or suspension based) and jelly capsules (of solutions or suspensions), as well as

liquid dosage forms or enemas, classified according to their volume into macro enemas (> 100 ml) or micro enemas (1-20 ml) (Murdan, 2013) . Absorption of drugs from aqueous and alcoholic solutions can occur very quickly, which has proven to be of great therapeutic value, for example in the rapid suppression of acute seizures with diazepam (McTague et al., 2018). On the other hand, absorption from suppositories is generally slower and very dependent on the formulation's characteristics: suppository base, the use of surfactants or other additives, active ingredient particle size, etc. In general, suppositories with water-soluble base (polyethylene glycol, glycerine) release the drug by dissolution, while low melting point fat bases should melt at body temperature to release the drug. Some suppositories contain an emulsifying agent that keeps the fatty oil

Other routes of medication administration

Pulmonary administration of inhaled drugs :-

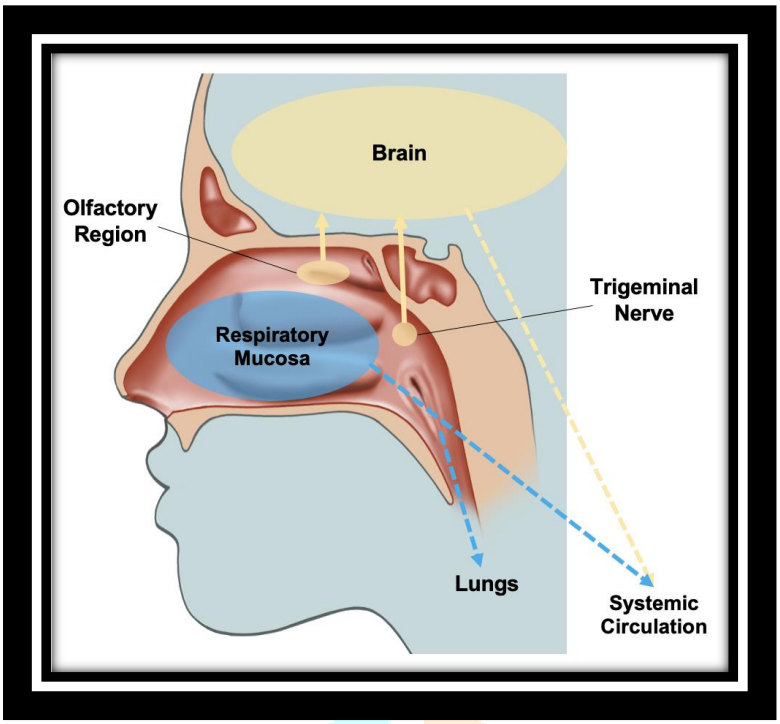
The pulmonary route of administration has been traditionally used for drug administration to the respiratory tract, in pathologies like chronic obstructive pulmonary disease or COPD, asthma, cystic fibrosis, etc. The main advantages of administering medications by inhalation include the rapid absorption and rapid onset of action (very important for bronchodilator and anti-inflammatory drugs, for example) as well as the localization of drug activity in the lung with minimal systemic toxicity, which is particularly important in the case of antiinflammatory corticosteroids such as beclomethasone, budesonide, fluticasone, etc. But it would be a mistake to consider the lungs as an administration site only suitable for the local effect of drugs. Indeed, the respiratory tract may also be regarded as a systemic administration route, as in the case of inhalable insulin (Peters and Hulisz, 2015). The lungs have a large surface area available for the systemic absorption of drugs: the alveolar-capillary 33 barrier. This is a highly permeable and highly irrigated membrane, less than 0.5 µm thick, with a surface area of around 100 m2 (Dagar, 2007) Human lungs, however, also have effective means for the elimination of deposited particles. In the upper airways, the ciliated epithelium contributes to mucociliary sweeping, by which the particles are drawn from the airways to the mouth. Already in the lungs, alveolar macrophages are able to phagocyte particles shortly after their deposition (Hickey, 2006). Thus, effective inhalation therapy, and especially when a prolonged action of the drug is desired, requires bypassing the lungs' clearance mechanisms for the drug to be completely absorbed. As for the pre-systemic losses of the drug, it is generally accepted that they are smaller by respiratory route than orally, but this is an aspect that must be addressed on a case-by-case basis. Although to a lesser extent, most metabolizing enzyme systems of the liver are also present in the lung. Bearing in mind that blood flow normalized to tissue weight is almost ten times greater in the lung, this organ may play a significant role in the overall systemic clearance of a drug (Farr et al., 1990). To be able to reach the lungs, through the bronchial tree, a drug must be in aerosol form, generated by an appropriate device. Aerosols are relatively stable two-phase systems consisting of condensed and finely divided matter suspended into a continuous gaseous phase. Due to the size restrictions imposed by this route (see Section 6.4.1.2), dispersion must be colloidal, and the dispersed phase may be a liquid (mist), solid (suspension) or a combination of both. There are three main devices for administering medications by inhalation (Garcia-Contreras

Pulmonary absorption of drugs :-

Depending on their size, insoluble particles, such as powder and microorganisms, may become trapped in mucous secretions or be rapidly phagocytosed by alveolar macrophages, mechanisms that ensure the sterility of alveoli despite the continuous inhalation of the microbes in the air. In contrast, compounds which are able to dissolve in the pulmonary 34 surfactant are capable of being absorbed by active transport and/or passive diffusion through both the aqueous pores and the epithelial membranes. Volatile and non-volatile lipophilic compounds are rapidly absorbed through the lipid membranes, and the substantial blood supply to the area ensures that the compounds are then rapidly transferred to the systemic circulation. The absorption of hydrophilic compounds is generally slower and tends to decrease as the molecular weight increases, being carried out through the aqueous pores present in the pulmonary epithelium. Certain hydrophilic compounds that do not absorb well by GI route, do it by the respiratory route, such as sodium cromoglycate and gentamicin (Farr et al., 1990). In addition, there are at least two pulmonary active transport systems, one for amino acids and one for organic anions. Sodium cromoglycate is transported by the latter, so it is considered that its absorption occurs both passively and actively (Nakamura et al., 2010). It should be taken into account that evaluating the pulmonary absorption of non-volatile compounds is a complex process, since usually only 5 to 20% of the administered dose reach the lungs by the use of aerosols, while other fraction may be swallowed and access the systemic circulation through the gastrointestinal tract, complicating the interpretation of the results.

Nasal route of drug administration :-

Nasal administration refers to the absorption of drugs across the nasal mucosa, i.e. not accessing to the respiratory tract. It is a form of administration that can be used for both local and systemic therapies and is presented as an alternative, non-invasive route, especially useful in the case of extensively metabolised or labile drugs in the GI medium. It is limited, however, to very small volumes (25-200 µl), and thus only applicable to potent drugs with high water-solubility. In addition, the active ingredient must have a molecular weight



Technological factors that influence the nasal absorption of drugs :-

In most nasal formulations, deposition site is controlled by adjusting variables such as particle diameter and size distribution, and the velocity of the aerosol particles.
Inspired particles are prone to downward pulling of gravity, and thus large, dense particles fail to deep penetrate into nasal cavity. Moreover, the impaction mechanism is most likely to occur when the air stream carrying an aerosol particle changes direction; due to the shape of the nasal cavity, deposition of particles predominates within the anterior nasal region, where there is very little absorption.
On the other hand, although the posterior nasal mucosa has greater permeability, depositing a drug in this area will involve a faster ciliary elimination. Therefore, it is accepted that drugs with slow absorption should be deposited in the anterior part of the nose, while those that are quickly absorbed should be deposited in the back of the nose (Rogerson and Parr, 1990).
The most commonly used dosage forms are solutions (nasal drops) and aerosols (nasal spray, both solutions and suspensions), although there are others, such as powder formulations, gel, creams or, more sophisticated, microspheres or liposomes. Drops are easy to formulate and apply, although it is difficult to control the applied dose. Conversely, aerosol formulations are packaged in suitable devices capable of delivering a well-defined dose. A key factor for the choice of the formulation type is the site of absorption preferred; aerosols are able to a deeper deposition of drugs than nasal drops.
Other factors that have to be considered are the pH, viscosity and osmolarity of the pharmaceutical formulation, as well as the presence of certain specialized excipients. With regard to the pH, it should be between 4.5 - 6.5 to avoid mucosa irritation. However, in the case of ionisable active ingredients, it may be considered to formulate at a pH outside that range to optimize their absorption by maximizing the proportion of the non-ionised form (Arora et al., 2002).
Drugs expulsion by the cilia may be reduced (at least to some extent) by the use of formulations with mucoadhesive materials (*e.g.* polyacrylic acid, cellulose polymers). They attach to the mucus layer prolonging the drug contact time with the epithelial surface.
Mucosal permeability modifying substances (absorption enhancers), such as bile salts, fatty acids, surfactants, chelants (such as EDTA), organic solvents (DMSO, ethanol), and others may also be employed. There are many mechanisms by which nasal absorption of a drug can be promoted, the most common being the reversible modification of the epithelial barrier structure. However, toxicological aspect is fundamental, since most of these substances are irritating, and there is no safety data regarding to their long term use (Cai et al., 2018).

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