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DRUG DELIVERY SYSTEMS AND BIOPHARMACEUTICAL CONSIDERATION OF DRUG PRODUCTS DESIGNS: AN REVIEW

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ABSTRACT

In the last few years, there have been numerous attempts to predict physicochemical properties that are most desirable for a good drug candidate. The drug discovery and development process for a typical research-based pharmaceutical company can be broken down into five distinct stages as described briefly below. At each stage, there will be several activities running in parallel, with the overall objective of discovering a candidate drug and developing to market as efficiently as possible. The strategic research of a particular company is usually guided by factors such as its inherent research competence and expertise, therapeutic areas of medical need, and market potential/commercial viability. Companies often wish to develop a portfolio of products within a specific therapeutic area to capture a segment of the market. If drugs are administered in solid dosage forms, they must be dissolved in the G.I tract before absorption can take place. For drugs with low solubility and high dose, the dissolution will be slow, and the dissolution rate will be the rate-limiting step for absorption. The G.I tract plays important roles in secretion, digestion, and absorption. Many biological factors such as gastric emptying, gastric and intestinal pH, GI content, GI motility, GI surface area, and blood flow can affect drug absorption. Several other routes such as parental, topical, rectal, respiratory and other novel approaches for product formulation and development enhance the biopharmaceutical consideration.

KEYWORDS: Oral route, Parental route, rectal route, pulmonary route, Topical route.

INTRODUCTION

Drugs are nearly administrated as pure chemical substances alone with formulated preparations or medicines. These can vary from relatively simple join to complex drug delivery system through the use of appropriate additive in the formulations. The excipients provide varied and specialized pharmaceutical functions. It is the formulation additive that amongst other things solubilizers, suspending agents, preservatives, emulsify, modify dissolution. Improve the compact ability to flavor drug substances to form various medicines or dosage forms. The principle objective of dosage form design is to achieve a predictable therapeutically response to a drug included in a formulation which is capable of large-scale manufacture with reproducible product availabity. Preservatives for avoid microbial contamination and also maintain physical and chemical stability. In addition factor governing choice of administration route and specific requirements of that route which affect that drug absorption need to be taken into account designing dosage forms. In addition factor governing choice of administration route and specific requirements of that route which affect drug absorption needed to taken into account when designing dosage forms. For example predrisolone are available in different dosage form like tablets, enteric-coated tablets, injection, eye drops and enema.

Dosage forms available for different administration routes

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

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

3) Therapeutic considerations including consideration of the clinical indication to be threatened and patient factors.

The major biopharmaceutical considerations in the design of drug products are

a. Pharmacodynamic consideration

Therapeutic objective, toxic effect and adverse reactions

b. Drug consideration

Chemical and physical properties of drug
c. Drug product consideration
Pharmacokinetics of drug, bioavailability of drug, route of drug administration, desired drug dosage form and desired dose of drug.

d. Patient consideration
Compliance and acceptability of drug product

e. Manufacturing considerations
Cost, availability of raw materials, stability and quality control.

Routes of drug administration[2-10]
Absorption pattern of drugs varies considerable by individual drugs substances as well as by the different administration routes like oral route, parentral route, rectal route, respiratory route, topical route are shown in Table 1**.** Variation in time of onset of action for different dosage forms are shown in Table 2.

Table.1

Onset action	Dosage Forms
Seconds	I.V injections
Minutes	I.M and S.C Injections , Buccal, Aerosols
Minutes - hours	injections, solutions, Suspensions, Powders, Capsules, Granules, Tablets, Modified release
Several hours	Enteric cotated Formulations
Days to weeks	Deopt injections, implants
Varies	Topical Preparations

Table2

Route of Administration	Dosage Form
Oral	Solution, Syrups. Suspensions, Emulsions, Gels, Powders, Granules, Capsules, Tablets.
Rectal	Suppositories, Ointments, Creams, Powders, Solutions.
Topical	Ointment, Creams, Pastes, Lotions, Gels, Topical Aerosols, Transdermal patches.
Parenteral	Injections (solutions, suspensions, Emusions forms) implants, irrigation & dialysis solutions.
Respiratory	Aerosol (solustions suspensions, emulsions, powders forms) inhalations, sprays, gases.
Nasal	Solutions, inhalations
Eye	Solutions, ointments, creams
Ear	Solutions, Suspensions, ointments, creams

I. ORAL PREPARATIONS

The major advantage of oral preparations is convenience of administration safety and elimination of discomforts involved with injections. The main disadvantage of oral preparation is the potential problem of reduced and erratic bioavailability due to either incomplete absorption or drug interactions and nausea with some drugs that cause local irritation. The ganglion-blocking drugs hexamethonium, pentolinium&bretylium are ionized at intestinal pH therefore; they are not absorbed orally to be effective. Neomycin, gentamicin & cefamandol[2], are not well absorbed orally. Drugs with large molecular weight are not well absorbed when given orally. For example: the drug cyclosporin has been given orally with good absorption when formulated with surfactant oil. A possible role of the oil is to stimulate the flow of lymph as well as to delay the retention of the drug oily vehicles have been used to lengthen the gastrointestinal transit time of oral preparations.

Absorption of lipid-soluble drugs: Most hydrophobic drugs are poorly soluble in water and generally not well absorbed orally because of failure of the drug to dissolve in the fluids of a G.I.T. Lipid-soluble drugs given with fatty excipients mix with digested fatty acid which are emulsified by bile in small intestine. The emulsified drug is absorbed through the gastrointestinal mucosa or through the lymphatic system. Fats are first hydrolyzed into monoglyceric and fatty acid by pancreatic lipase. The fatty acids then react with carrier lipoproteins to form chylomicrons which absorbed through lymph. The chylomicrons eventually release the fatty acids and any lipophilic drugs are incorporated in the oil phase. Calcium carbonate, a source of calcium for the body was only about 30% available in a solid dosage form, but was almost 60% bio available when dispersed in a special vehicle as a soft gelatine capsule. Many oral adminstratered drugs are irritating to the stomach. Drugs may cause nausea or stomach pain when taken on an empty stomach. A common drug that causes irritation is aspirin; buffered aspirin tablets, enteric coated tablets & granules are available. Enteric coating may sometimes delay or reduce the amount of drug absorbed enteric coating may not abolish gastric irritation completely.

Large amount of antacids or buffering material is included in the formulation, dissolution of aspirin may occur quickly leading to reduced irritation to the stomach. Certain drugs have been formulated into soft gelatin capsules to improve drug bioavailability and reduce gastrointestinal side effects. Soft gelatin capsules cures less irritation. There are many options available to the formulation to improve the tolerance of the drug and minimize gastric irritation. The nature of excipients and the physical state of the drugs are important and must be carefully assessed before a drug product is formulated. Some excipents may improve the solubility of drug facilitate absorption.

BUCCAL AND SUBLINGUAL ROUTE

- **Buccal route**: The medicament is placed between the cheek and the gums. Sublingual route: the drug is placed under the tongue and allowed to dissolve are shown in fig 1.

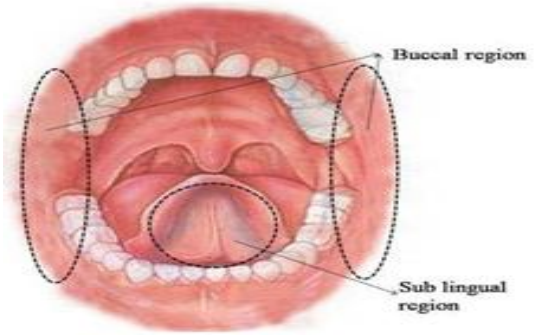


Fig.1

A drug that diffuses and penetrate rapid across mucosal membrane may be place under the tongue and rapidly absorbed. The tablet designed for release under the tongue is called sublingual tablet nitroglycerins, isoproterenol, erythrithyl tetranitrate, isosorbide dinitrate. A newer approach to drug absorption from the oral cavity has been development of a trans lingula nitroglyceryl spray. The spray containing 0.4 mg per metered dose is given by spraying 1or 2 metered doses on to the oral mucosa at the onset of an acetate angina attack. The barrier to drug absorption from this route is the epithelium of oral mucosa.

Advantages

- Rapid absorption and higher blood levels due to high vascularisation of the region & therefore particularly useful for administration of antianginal drugs.
- No first pass hepatic metabolism
- No degradation of drugs such as that encountered in the GIT
- Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.

FACTORS TO BE CONSIDERED IN THE ORAL MUCOSAL DELIVERY

Lipophilicity of drug: Slightly higher lipid solubility than that required for gastrointestinal absorption is necessary for passive permeation.

Salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i,e biphasic solubility. Of drug is necessary for absorption, absorption is delayed if the mouth is dry.

pH of the saliva: Usually around 6, the buccal pH favours absorption of drug which remains unionized.

Binding to oral mucosa: Systemic availability of drug that binds to oral mucosa is poor.

Storage compartment: Some drugs such as buprenouphine,a storage compartment in the buccal mucosa appears to exisit which isresponsible for the slow absorption of drugs.

Thickness of oral epithelium: Sublingual absorption is faster than buccal since the epithelium of former region is thinner & immersed in a larger volume of saliva. Examples of drug administered by oral mucosal route includes antianginal like nitrites antihypertensives like nifedipine, analgesics like morphine and bronchodilators like fenoterol.

Factors modifying drug action

Age: Important physiological difference from adult In elderly ,renal function progress declines so that g.f.r is~75% to 50% years &~50% to 70 years age compared to young adults. On BW or BSA basis & for many drugs manufacturer give dosage recommendation on mg/kg basis. There is also a reduction in the hepatic microsomal drug metabolizing activity and liver blood flow oral bioavailability of drugs with high hepatic extraction is generally increased, but overall effects on drug metabolism not uniform due to lower renal a well as metabolic clearance. The elderly are prone to develop cumulative toxicity while receiving prolonged medication.

Sex: Females have smaller body size and required doses that are on the lower side of the range. Subjective effect of drug may differ in females because of their mental makeup. Maintenance treatment of heart failure with digoxin is reported to be associated with higher mortality among women then among men. A number of antihypertensive interfere with sexual function in males but not in female. Gynaccomastia is a side effect of ketoconazole, metoclopramide, chlorpromazine that can occur only in men. Ketoconozole cause loss of libido in men but not in women. Drug given during pregnancy can affect the foetus. There are marked and progressive physiological changes during pregnancy, especially in the third trimester which can alter during disposition. Gastrointestinal motility is reduced. Delayed absorption

of orally administered drug. Hepatic microsomal enzymes undergo induction many drugs are metabolized faster.

G.I. Mobility: GI mobility must be optimal for absorption of oral drugs, it should be neither increased nor decreased which may affect the rate or extent of absorption. Different diseases or drugs may alter the mobility.

Functional integrity of absorptive surface: Flattening and edema of mucosa decrease absorption. Dysfunctional breach in the skin affects the absorption of topical drugs. Para sympathomimetic drugs can decrease drug absorption and parasympatholytic drugs can increase absorption, metoclopramide prevents vomiting and accelerates gastric emptying.

Gastrointestinal diseases: These can alter absorption of orally administered drugs. The changes are complex and drug absorption can increases or decreases for example disease absorption of amoxicillin is decreased but that of cephalexin and cotrimoxazole is increased. Thus, malabsorption syndroms dose not necessarily reduce absorption of all drugs. Gastric stasis occurring during migraine attack retards the absorption of ingested drug.

Liver diseases: Liver diseases can influence drug disposition in several ways bioavailability of drugs having high first pass metabolism is increased due to loss of hepatocellular function. Serum albumin is reduced protein binding of acidic drugs. Prodrugs needing hepatic metabolism for activation.

II. PARENTERAL PREPERATIONS[11-23]

The parenteral route introduces drugs directly across the body's barrier defenses into the systematic circulation or other vascular tissues shown in fig. 2. This refers to administration by injection which takes the drug directly into the tissues fluid or blood without having to cross the intestine mucosa. Parenteral routes can be employed even in unconscious. Unconscious patient. There are no chances of interference by food or digestive juices liver is by passed. Disadvantages of parenteral routes are the preparation has to be sterilized and is costlier, the technique is invasive and painful, and assistances of another person is mostly needed. There are chances of local tissues injury and, in general parenteral route is riskily then oral the important parenteral routes are.

- Subcutaneous, intramuscular, intravenous, intradermal injection, intra articular, intra synovial, itra spinal, intra arterial, intra cardiac, intracisternae, intraperitoneal, intrapleura, intrathecal

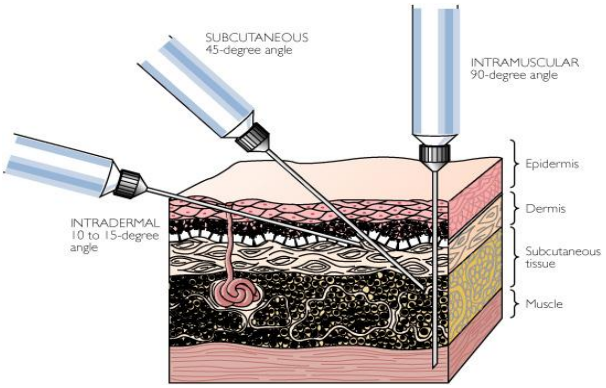


Fig 2: parenteral routes

1. Subcutaneous

The drug is deposited in the loose subcutaneous tissues which is richly supplied by nerves (irritant drugs cannot be injected) but is less vascular (absorption is slower than intramuscular).

Only small amount can be injected S.C self injection is possible because deep penetration in not needed.

Some special forms of these routes are

A). Dermoject: In this method needle is not used a high velocity jet of drug solution is projected from a microfineorifice gum like implement are shown in fig.3. The solution passes through the surfacious layers and gets deposited in the subcutaneous tissues. It is essential painless and suited for mass inoculations.

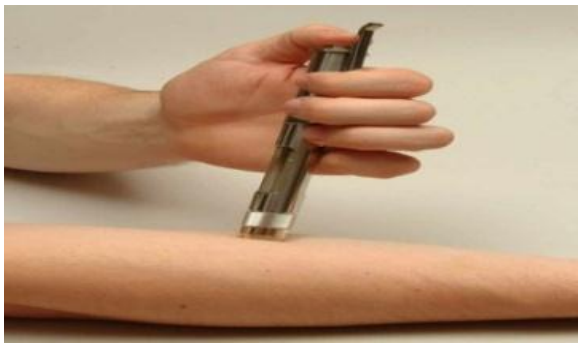


Fig 3: Dermoject

B). Pellet implantation: The drug in the form of a solid pellet is introduced with a trochar and cannula shown in fig4. This provides sustained release of the drug over weeks and months. Eg: DOCA, testosterone.

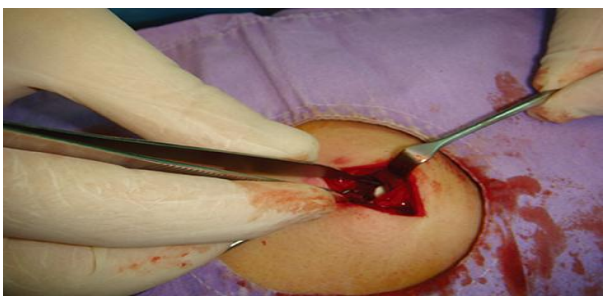
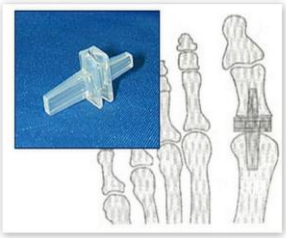


Fig 4: Pellet implantation

C). Sialistic and biodigradable implants
Crystalline drug is packed in tubes or capsules made of suitable materials and implanted under the skin. Slow and uniform leaching of the drug occur over months providing constant blood levels shown in fig.5,6.



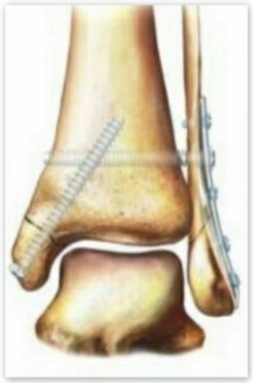


Fig.5: Sialistic implants Fig.6:Biodegradable implants

Factors affecting on subcutaneous route absorption
All factors that influence in drug absorption are also applicable to absorption form subcutaneous site.

Factors
1) Vascularity of the injection site
2) Lipid solubility and ionization drug.
3) Molecular size of the drug.
4) Volume of injection and drug concentration.
5) pH, composition and viscosity of injection vehicle.

2. Intra muscular
The drug is injected in one of the large skeletal muscles-deltoid, triceps, glutinous maximus, rectus fenmoris shown in fig. 7.

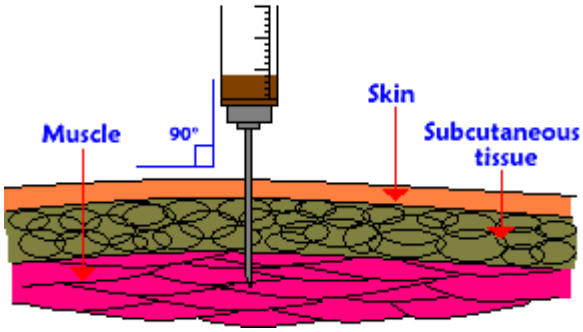


Fig 7: Intramuscular

Muscle is less richly supplied with sensory nervous (mild irritant can be injected) and is more vascular (absorption of drugs in aqueous solution is faster). It is less painful, but self injection is often impracticable because deep self injection is often depot preparation (oily solution, aqueous solutions) can be injected by this route intramuscular injection should be avoided in anticoagulant treated patients because it can produce local hematoma. Factors affecting on drug absorption on intra muscular route.

Absorption of drug from I.M site is relatively rapid but much slows an incomprison to I.M injections. Factors that determine rate of drug absorption from I.M sites are

Factors
1) vascularity of the injection site the decreasing order of blood flow rate to muscular tissue in which drugs are usually injected is : arm (deltoid)>high(vastuslaterals)>buttock(gluteus Maximus).
2). Lipid solubility and ionization of drug high lyophilic drugs are absorbed rapidly by passive diffusion where as hydrophilic and ionized drugs are slowly absorbed through capillary pores.
3). Molecule size of the drug.
4). pH composition and viscosity of injection vehicle.
5).volume of the drug injection and drug concentration.

3. Intravenous
The drug is injected as a bolus or infused slowly over hours in one of the superficial veins. The drug reaches directly into the blood streams and effects are produced immediately shown in fig.8.

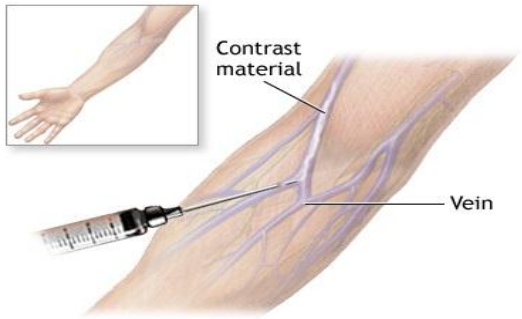


Fig 8: Intravenous

- Drugs given directly into a vein produce very rapid action and the desired blood concentration can be obtained rapidly with a smaller dose. The titration of dose is possible.
- A drug may be injected as a bolus, in an infusion and isotonic glucose or saline.
- The injection should be given slowly in case of certain drugs such as iron and aminophylline, as a sudden high blood concentration may be dangerous.

Disadvantages
- Once the drug is administered by this route, its action cannot be halted.
- Local irritation can lead to phlebitis
- Self-medication is difficult.

4. Intradermal injection
The drug is injected into the skin for vaccine, sensitivity testing or scarring, multiple puncture of the epidermis

through a drop of the drug is done this rate is employed for specific purposes only shown in fig.9.

Purpose: injects medication below the epidermis drugs are absorbed slowly. Typically used for diagnosis of tuberculosis and allergens.

Site: inner aspects of forearm: UPPER CHEST

Angle of insertion: 10^0-15^0

Maximum dose: 0.01 to 0.1ml.

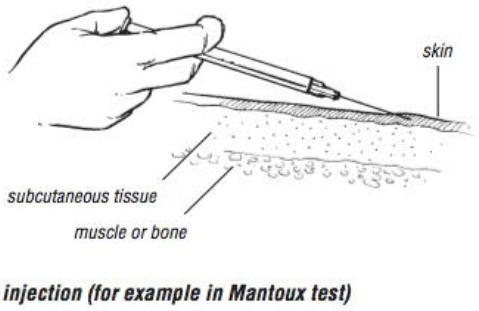


Fig 9: Intradermal

Intradermal injection also known as the mantoux method. As currently administrated typically uses a 27 gauge 10-mm needle that is inserted parallel to the skin surface about 3mm until the entire level is covered. Intradermal injection has been validated as a safe and effective method of immunization based on our experience with small pox, tuberculosis and other vaccines. A microneedle based intradermal injection is inserted perpendicularly in the skin and is reported to be painless. Intradermal vaccine delivery very often results in more potent immune response then vaccine administrated by intramuscular or subcutaneous route. A number of methods for intradermal vaccine delivery have been developed. The standard intradermal injection technique developed a century ago by mantoux.
Intradermal injection is delivered into the dermy or the skin layer underneath the epidermis. The dermis is on most places of the human body, only a few mm thick.

Method of intradermal injections
a. With a normal sized needle.
b. With shooter needle.
c. Without needle.

5. Intrathecal administration
Intrathecal administration is a roof of administration for drugs via an injection in to the spinal canal especially into the subarachnoid space so that it reaches the cerebrospinal fluid and is useful in spinal anesthesia, chemotherapy or pain management applications shown in fig10.

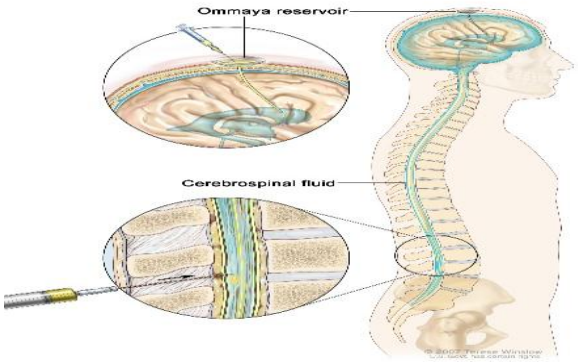


Fig 10: Intrathecal

This route is also used to introduce drugs that light certain infections, particularly post neurosurgical. The drug needs to be given this way to avoid the blood brain barrier the same drug begin orally must enter the blood stream and may not be able to pass out and into the brain. Drugs given by the intrathecal route often have to be made up especially by a pharmacist or technician because they cannot contains any preservative harmful inactive ingredient that is sometimes found in standard injectable drug preparations. The route of administration is sometimes simply referred to as "intrathecase"however the terms is also an adjectives that refers to something occurring in or introduced in to the anatomic space or potential space inside a sheath most commonly the arachnoidmembrane of the brain or spinal card.

III. RECTAL DRUGS
The human rectum represents a body cavity in which drugs can be easily introduced and retained and from which absorption is well possible. In some cases nausea, vomiting, this route of rectal drug administration is preferable. The main drawbacks of rectal drug administration including the interruption of absorption by defecation and lack of patient acceptability. Rectal administration uses the rectum as a route of administration for medication and other fluids. The rectal drugs which are absorbed by the rectums blood vessels and flow into the body's circulatory system. Which distributes the drug to the body's organs and bodily systems. A drug is administered rectally will in general have a faster on set of action, higher bioavailability by administrating a drug rectally is that it tends to produce less nausea, compared to the orally and prevents the loss of drug due to EMESIS. The rectal route drug administration in 3 routes:1) Metabolism 2) Systemic 3) Portal

This means the drug will reach the circulatory system with significantly less alteration an greater in concentrations. The rectal of route administration is useful for the patients who cannot swallow the drugs. Because using the rectal route enables a rapid, safe and lower cost, alternative to administration of medications. This route of drugs administered by the patients like long

term care, as an alternative to intravenous (or) subcutaneous medication delivery in other instances.

METHODS

- A rectal bulb syringe that can be used to introduce fluids into the rectum.
- A suppository, a drug delivery system inserted into the rectum.
- An enema, the act of introducing a liquid-drug solution dissolved in water, the amount usually being<10ml into the rectum and some times in the colon.
- A specialized catheter designed for rectal administration of medications and liquid that can be placed safely and remain comfortability in the rectum for repeated use. The rectum has neumerous amounts of blood vessels available to absorb drugs. Products for rectal drug delivery may be administered either in solid or liquid dosage form. Rectal drug administration can be for either local or systemic drug delivery.
- A sustained release preparation may be prepared for rectal administration. The rate of release of the drug from this preparation is dependent on the nature of the base composition and on the solubility of the drug involved. Rectal drug absorption may partially bypass the first pass effects due to enzymes in the liver. A water soluble base such as polyethylene glycol, glycerin generally dissolves and release the drug. An oleaginous base with low melting point may melt at body temperature and release the drug. Some suppositories contain emulsifying agents that keep the fatty oils emulsified and the drug dissolved in it.
- Rectal drug delivery is generally for local drug delivery, but some systemic drug absorption can occur. Progesterone vaginal suppositories have been evaluated for the treatment of premenstrual symptoms of anxiety and irritability. Anti fungal agents are often formulated into suppositories for treating vaginal infections.

Rectal drugs absorption

- Water soluble drugs can be easily administrated by this rectal route.
- Some drugs are only soluble in oil like (kannabis) need more preparation but can effectively administrated via this rectal route after extraction into a suitable medium or in a suppository form.
- The mechanism of rectal drug absorption from the rectum is probably no difference to that in the upper part in the GIT, despite the fact that the physiological circumastances differ substantially absorption from aqueous and alcoholic solutions may occur very rapidly.
- The absorption from suppositories is generally slower and very much dependent on the nature of the suppository base.
- There is some evidence that hepatic first pass elimination of high clearance drug is partially avoided after rectal administration.

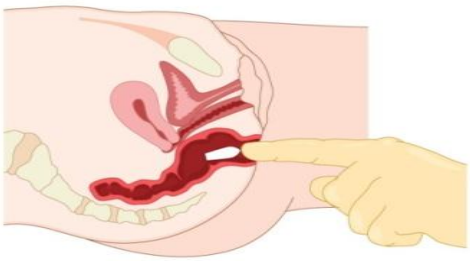


Fig.11

Advantages

- Some irritant and unpleasant drugs can be introduced into rectum as suppositories.
- This route can also be useful in the patient is having recurrent vomiting or unconscious stage.
- Generally less drug degradation via this route of administration.
- The dose can be retrieved if necessary.
- There is the potential of long term drug absorption with various intrauterine devices (IUDs).
- When a drug is ingested normally it is absorbed by the intestine.
- The molecules are drained through vein to the liver.
- All the intestine venous system goes to the liver, except for the rectum.
- The venous system of rectum goes to iliac vein which extends to the vena cava and then to the heart.

Disadvantages

- This is rather inconvenient and embarrassing.
- Absorption is slower, irregular and unpredictable.
- Rectal inflammation can result from irritant drugs.
- Rectal mucous membranes are very sensitive .when the introduction of drugs may irritate the rectum.
- Erratic absorption-drug absorption from a suppository is often incomplete and erratic.
- They bleeding problems such as discomfort to real pathologies.

IV. PULMONARY DRUG DELIVERY SYSTEM

Pulmonary route was use to treatment of different respiratory diseases. The inhalation therapies involved the use of leaves from plants vapors from aromatic plants, balsams, and myrrh. The invention of liquid nebulizers, these newer treatments developed into valid pharmaceutical therapies.

RECENT TECHNOLOGIES OF PULMONARY DRUG DELIVERY

Nebulizer: Now a days the many physicians are mostly use nebulizer for the treatment of acute asthma in an emergency care unit or for treating patients with severe asthma at home. Injet nebulizers, an aerosol is prepared by a high velocity air stream from a pressurized source directed against a thin layer of liquid solution. Ultrasonic nebulizer includes the vibration of a piezoelectric crystal

aerosolizing the solution. The nebulizer can transport more dose shown in fig.12.

Fig.12

Metered Dose Inhaler (MDI): These are the most common device for administration of aerosolized drugs. In this technique, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in exact measured amounts upon actuation of the device are shown in fig.13.

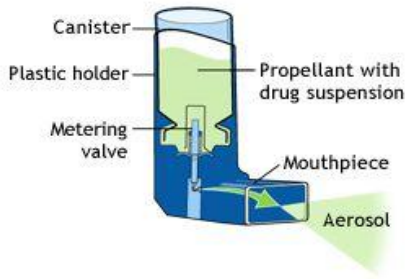


Fig.13

Powder Inhaler (DPI): Dry powder systems use drug single or its blends with a suitable carrier mainly as lactose, for delivery to the lungs. The three main factors Drug, Carrier, and device may affecting the act of pulmonary delivery of drugs. Unlike MDIs, delivery of medication with a DPI requires minimum patient coordination and collaboration of breathing following actuation of the device. In addition, DPIs are small, portable devices that can be easily carried in a purse or pouch. There is also not requiring using spacers. In addition, DPIs are devoid of environmentally injurious CFC propellants.

CONCLUSION

Drug absorption is a complicated process in which many physiological and physiochemical factors are involved. Understanding the principles of drug absorption benefits the designing of formulation strategies to enhance the bioavailability and *in vivo* drug activity. In summary, drug absorption mechanisms include passive diffusion and active transport. Permeability, solubility, and dissolution, GI physiological conditions, and dosage forms can influence the drug absorption rate. In general, if a drug has high water solubility and low membrane permeability (hydrophilic drugs), permeability usually limits absorption, unless it is carrier mediated or paracellular absorption dependent. Strategies which can enhance the drug permeability in dosage design could be used to increase this permeability controlled drug absorption.

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