



Alternative Routes of Drug Administration- Transdermal, Pulmonary & Parenteral

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ABSTRACT: Oral Route is considered to be the most common route of drug delivery to obtain a systemic effect. However, with the recent developments in the field of drug delivery, it has been found that delivery through alternative routes is sometimes more beneficial. This article deals with the salient features, advantages and disadvantages of some of the alternative routes of drug administration- Transdermal, Pulmonary and Parenteral routes. Though the mechanisms of action of drugs delivered by these routes are different, they offer a common advantage- increased Therapeutic Index with simultaneously decreased side effects. The latest innovations in drug formulations delivered through these routes have also been discussed. © 2011 IGJPS. All rights reserved.

KEYWORDS: Transdermal; Pulmonary; Parenteral; Vesicular Carrier Systems; Drug Delivery.

INTRODUCTION

At present, the most common route of drug delivery is Oral Route. While it has the notable advantage of ease of administration, it also suffers from many drawbacks such as erratic and variable absorption of drug(s), poor bioavailability due to first pass metabolism, variable drug concentrations in the body leading to greater chances of adverse effects or therapeutic failure. To overcome all these limitations and to provide a continuous steady rate of drug at the site of action, novel therapeutic systems were developed [1]. This article describes the three other major routes of drug delivery i.e. Transdermal, Pulmonary and Parenteral routes, along with their merits, demerits and recent advances.

TRANSDERMAL/TOPICAL

The word Transdermal has been derived from the root *Trans* meaning through, across or beyond and *derma* meaning skin. Thus, transdermal therapeutic systems are defined as a type of dosage form which when applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation.

Mechanism & Pathways of Drug Penetration

Although the skin has many histologic layers but in general, it is described in terms of three major tissue layers: the epidermis, dermis and the hypodermis.

The outermost layer, the **epidermis**, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. The epidermis consists of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale (from outermost to innermost). If the drug is able to penetrate the stratum corneum, it can enter the blood stream. Beneath the epidermis, the **dermis** contains a system of capillaries, nerves as well as the epidermal appendages such as hair follicles, sebaceous glands and sweat glands. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer drugs across this layer [2]. **Hypodermis**/ Subcutaneous tissue is simply a layer of fat.

The drug enters the systemic circulation through a process known as **Percutaneous Absorption** which involves the passive diffusion of substances across the skin. This permeation of drug can take place through:

1. Passage through epidermis itself (Transepidermal)[2]
2. Diffusion through widely distributed hair follicles and sweat glands (Transfollicular)[2]

Transepidermal Absorption

Permeation through the transepidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The stratum corneum develops a thin, tough, relatively impermeable membrane which usually provides the rate limiting step in transdermal drug delivery system. The epidermal cell membranes are tightly joined and there is no intercellular space for ions and polar non-electrolyte molecules to pass through. Thus, permeation requires frequent crossings of cell membranes and to do that, drugs should be engineered such that they are both water soluble and lipid soluble. The best combination is the drug being 50 per cent water soluble and 50 per cent lipid soluble. This is because “Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass through the skin because of hydrated intracellular proteins”. Using drugs engineered in this manner, much more rapid and useful drug delivery is possible [2].

Transfollicular Absorption

The skin's appendages offer only secondary avenues for drug permeation. Sebaceous and eccrine glands are the only appendages which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. The drug can move into the body through sebaceous or eccrine glands and the hair follicles. Though eccrine glands are numerous, their orifices are tiny and add up to a miniscule fraction of the body's surface. Moreover they are so profusely active that molecules can't diffuse inwardly against the gland's output. For these reasons they are not considered as a serious route for percutaneous absorption. However since the opening of the follicular pore, where the hair shaft exits the skin, is relatively large and sebum aids in the diffusion of penetrants, the follicular route remains an important avenue for percutaneous absorption [2].

Topical Drug Delivery System-Transdermal Patches

These are devices in the form of adhesive patches of various shapes and sizes which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum. The drug is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the under surface of which is smeared with an adhesive. This patch is then worn on the skin for an extended

period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. The micropore membrane is such that the rate of drug delivery to skin surface is less than the slowest rate of absorption from skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow [3].

Transdermal drug absorption can considerably change drug kinetics. It depends on a variety of factors including the following [4-15]:

- [1] Site of application
- [2] Thickness and integrity of the stratum corneum of the epidermis
- [3] Permeability of the membrane
- [4] State of skin hydration
- [5] Size of the molecule
- [6] pH of the drug
- [7] Lipid solubility
- [8] Drug metabolism by skin flora
- [9] Depot of drug in skin
- [10] Alteration of blood flow in the skin by additives and body temperature

A number of drugs can be administered transdermally. For example, scopolamine patches to check motion sickness and fentanyl patches to treat cancer pain or chronic pain syndromes are being used currently by the transdermal route [12, 14].

Advantages

This route is becoming increasingly popular due to the following reasons [2, 16]:

- [1] Provides smooth plasma concentrations of the drug without fluctuations, for a long period.
- [2] Minimizes inter-individual variations as drug is subjected to little first pass metabolism
- [3] Fewer side effects thereby increasing the therapeutic value of many drugs.
- [4] Equivalent therapeutic effect can be elicited with less amount of dose if given as a transdermal patch as compared to dose of same drug if given orally.
- [5] Drug intake can be stopped at any point by simply removing the transdermal patch.
- [6] Self- administration is possible.
- [7] Patient compliance is better as many patients prefer transdermal patches to oral tablets of same drug.

Disadvantages[2,17]

- [1] Only lipophilic drugs can effectively cross the stratum corneum and hence the drugs must have some desirable physicochemical properties for penetration. Hydrophilic drugs will not be able to reach the systemic circulation unless modified to some suitable form.
- [2] Doses of only 5mg or less can be administered in a day.
- [3] Large numbers of excipients used may cause rashes, local irritation, erythema or contact dermatitis. E.g.: Scopolamine patches are used to treat motion sickness or to prevent nausea and vomiting. However, excessive uptakes through the skin and rubbing of the patch on the eye have resulted in mydriasis [12].
- [4] The patch may be uncomfortable to wear as adhesives may not adhere well to all types of skin.
- [5] High cost of product.

Vesicles as a Tool for Transdermal Drug Delivery

Despite the many advantages of skin as a site of drug delivery, only a few drugs such as clonidine, estradiol, nitroglycerine, fentanyl, testosterone, scopolamine, nicotine, oxybutinin are commercially available. The most important reason for this is the low permeability of drugs in the stratum corneum. One approach to increase this rate is the use of vesicle formulations.

Structure of Conventional Vesicles

Vesicles are basically water filled colloidal particles. They consist of amphiphilic molecules in a bilayer conformation. Hydrophilic drugs can be entrapped into the aqueous compartment, whereas amphiphilic, lipophilic drugs can be associated with the vesicle bilayer. Vesicles are most commonly composed of phospholipids or non-ionic surfactant known as liposomes and niosomes respectively.

But here also a problem arose as liposomes and niosomes are highly rigid in nature and hence very less efficient in enhancing the drug transport across the skin. Therefore, the need of elastic and ultra-deformable vesicles arose, to combat the stratum corneum barrier and affect a good transport across the skin [18, 19].

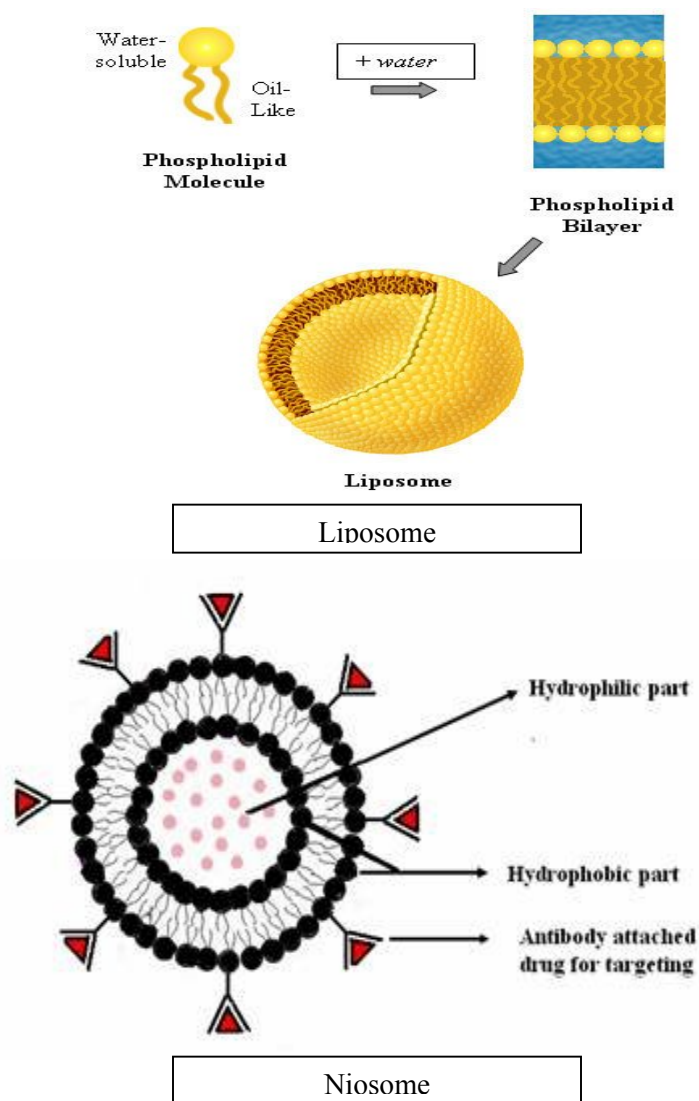


Fig.1

Structure of Ultradeformable Vesicles

These vesicles consist of a micelle forming and a bilayer forming surfactant as destabilizing and stabilizing portions respectively. When two or more compartments with a sufficiently different affinity for curved surfaces are combined into one membrane, the more polar of them tend to accumulate in more strongly curved portion while the less polar have more affinity for smaller curvature. This permits molecular rearrangement upon any deformation in the membrane [20].

PULMONARY

The structure of the airways, with rich capillary bed of the alveoli, allows air to come in close contact with the blood. This makes drug administration through the airways, in the form of inhalation or aerosol, a useful route. Inhalation therapies have been used successfully for years, providing rapid relief for respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD) [21].

Advantages[21,22]

- [1] Dose can be removed without the risk of contaminating the remaining material in the container.
- [2] There is greater protection against drug degradation by oxygen and moisture, so stability is increased for labile substances.
- [3] While dispensing a dose, sterility can be maintained in case it is an important factor.
- [4] Direct delivery of the medication to the affected area in the desired form is possible.
- [5] As compared to topical application, irritation produced by mechanical application is reduced or eliminated.
- [6] It is easy and convenient to apply the formulation.
- [7] The medication can be applied in a thin layer.
- [8] Drug solubility issues can be solved by using lipid, water or lipid/water emulsions as drug carriers. Thereby, viscous drug formulations can also be nebulized.
- [9] Nebulized liposomal drug formulations are stable.
- [10] Protein-containing solutions can be nebulized

Disadvantages [21]

- [1] The transport of drug to the site of action is not guaranteed.
- [2] There may be drug irritation and toxicity.
- [3] Drug retention and drug clearance may be a problem.
- [4] Drug may not be stable in vivo.
- [5] Targeting specificity is questionable.

Techniques Used for Drug Administration by Pulmonary Route

Two techniques can be used for administration of drugs by pulmonary route: aerosol inhalation (which is used in intranasal administration) and intratracheal instillation. Intratracheal administration is a simple, non-expensive process, but the distribution of drugs is non-uniform. On the other hand, aerosol administration is costly and there is difficulty in measuring the exact dose, but drug distribution is more uniform and penetration into the alveoli is greater [21].

Aerosols

An aerosol or pressurized package is defined as “a system that depends on the power of a compressed or liquefied gas to expel the contents from the container”. The components of the aerosol package are the container, valve and actuator. Aluminium, tin plate, stainless steel or glass (uncoated or plastic coated) containers may be used. Containers must be able to withstand pressure of 140-180 psig at 130oF. For pharmaceutical products, the valves are expected to expel a given amount of the medicated aerosol. The valves used are continuous spray valves or metering valves. An actuator is fitted to the valve stem to ensure that the aerosol is delivered in the proper form. The different types of actuators are: spray, foam, solid-stream or special actuators. Aerosols may be formulated as solution, water-based, suspension and foam systems [22].

The drug particles delivered by aerosols can be deposited in the respiratory tract by: Interfacial interception, Brownian diffusion, Gravitational sedimentation and Impaction [23].

Interfacial Interception: It occurs when a particle contacts an airway surface due to its size or shape. Interception mostly occurs in small airways. It is significant in the case of fibers as they easily contact airway surfaces due to their length. Also, they can often reach the smallest airways [23].

Brownian Diffusion: Diffusion is the major mechanism of particle deposition when the particle size is less than 0.5 μ in diameter. Diffusion is due to the transport of particles from a region of high concentration to that of low concentration due to Brownian motion. Diffusion is most likely to occur in the smaller airways of the pulmonary (alveolar) region [23].

Gravitational sedimentation: Sedimentation involves settling of the particles in the smaller bronchioles and alveoli. The terminal settling velocity of the particles determines their rate of sedimentation [23].

Impaction: When there is a bifurcation in the airways, the direction of the airflow changes. The suspended particles tend to travel along their original path due to inertia and may impact on the airway surface. Stopping for smaller particles is very low. Impaction mostly occurs in case of larger particles. Deposition by it is largely in the bronchial region [23].

Some of the drugs used for pulmonary drug delivery are as follows. β -adrenergic agents (like salbutamol, terbutaline, albuterol), anticholinergics (like ipratropium bromide) and steroids & other anti-inflammatory agents (like beclomethasone, dexamethasone, cromolyn), for asthma. Antibiotics (like tobramycin, erythromycin) and antibacterial agents (like ciprofloxacin, ofloxacin), for pulmonary infections. Anticholinergics, β -adrenergic agents, corticosteroids, antiproteases (like al-antitrypsin), and cystine derivatives (like acetylcysteine), for COPD. Antianginal agents (like nitroglycerine) and antihypertensives (like nifedipine), as cardiovascular agents. Antidiabetics (like insulin) and hyperglycemic agents (like glucagon), as blood glucose modifiers. Antidiuretic hormone (like desmopressin), gonadotropin releasing hormone, growth hormone releasing hormone, leutenizing hormone and premenstrual tension formulations (like progesterone, vasopressin) are some hormone formulations. Some other applications are as antidotes, antivirals, antihistaminics, immunizing agents and in gene therapy [24].

Aerosols are delivered mainly by three delivery systems: metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers [24].

1. MDIs

MDIs were the most frequently used of the aerosol drug delivery systems. However, over the years, several problems with their usage have been found. Some of these are: only a small fraction of the drug escaping the inhaler actually reached the patient's lung; the suspended particles in propellants were unstable and valve designs were suboptimal, leading to irreproducible dose metering; potentially carcinogenic compounds in low concentrations were found to be extracted from valve components by the propellant system and inhaled by the patient; pressurized MDIs depended largely on Chloro Fluoro Carbon (CFC) propellants, which have been associated with depletion of the ozone layer. These have led to new designs of devices, improved formulations and valves, and switching over to environment friendly propellants [24].

The MDI contains three basic ingredients: drug, one or more propellants, and a surfactant [21]. The propellant is responsible for developing the proper pressure inside the container, and in expelling the product when the valve is open. It also helps in the production of foam or atomization of the product. The most commonly used propellants for inhalation use are fluorinated hydrocarbons such as trichloromonofluoromethane (Propellant 11), dichlorodifluoromethane (Propellant 12), and dichlorotetrafluoroethane (Propellant 114). For pharmaceutical use, blends of various fluorocarbon propellants are generally used, e.g. 12/11 in the ratio of 50:50, 12/114 in the ratio of 40:60 [22]. An alternative propellant to CFCs is 1, 1, 1, 2- tetrafluoroethane (HFC-134a). In addition, investigations on other non-chlorinated propellants, including 1, 1, 1, 2, 3, 3, 3- heptafluoropropane, are being done [24]. The surfactant is added to aid in the dispersion of suspended drug particles or dissolution of a partially soluble drug [21]. A co-solvent may or may not be used to aid drug dissolution. Flavors and suspended sweeteners may be added. Stabilizing agents such as antioxidants or chelating agents may be present in formulations containing dissolved drug. In an MDI, metering valve is present. Spacer device may be present, which increase the distance between the spray orifice and oropharynx, thereby preventing complete oropharyngeal deposition [24].

2. DPIs

In the Dry Powder Inhalers, dry particles are dispersed as an aerosol. The basic components of a DPI are: the drug powder and other powdered excipients if necessary, a drug reservoir or premeasured individual doses, the device body, and a cover (to prevent entrance of dust or moisture) [24]. DPIs deliver the dry drug powder directly into the lungs and can be employed locally for treatment of respiratory diseases [25]. A wide range of DPIs are available in the market, from single-dose devices to a variety of multiple-dose devices. Lung deposition varies among these DPIs. About 20-25% of the drug is retained within the device, while approximately 12-40% is of the emitted dose is delivered to the lungs [26, 27, 28, 29]. Inefficient deaggregation of the finer drug particles from coarser carrier lactose particles or drug pellets may cause poor drug deposition with DPIs [26, 30, 31]. A DPI type of an aerosol is created by directing air through loose powder. Most DPI particles are large due to large powder agglomerates or the presence of large carrier particles, because of which they do not penetrate into the lungs. Thus, creation of a turbulent air flow in the powder container determines dispersion of the powder into respirable particles. The turbulent air stream aids in breaking up of the aggregates into small particles which can be carried into the lower airways and also helps to separate carrier from the drug [26, 32].

3. Nebulizers

The two common types of nebulizers are, air-jet and ultrasonic. The jet nebulizer works on the Bernoulli principle. In this, a compressed gas, which may be air or oxygen, passes through a narrow orifice creating a low pressure area at the outlet of the adjacent liquid feed tube, which results in the drawing up of a drug solution from the fluid reservoir and its shattering into droplets in the gas

stream. On the other hand, the ultrasonic nebulizer uses a piezoelectric crystal which vibrates at a high frequency of 1-3 MHz to generate a fountain of liquid in the nebulizer chamber. Treatments using jet nebulizers are time-consuming and inefficient, with large amounts of drug wastage. Besides, most of the drug never reaches the lung. Approximately, only 10% of the dose is actually deposited in the lungs. The major proportion of the drug is either retained within the nebulizer (dead volume) or released into the environment during expiration. Further, the physical properties of the drugs like, viscosity, ionic strength, osmolarity, pH & surface tension may limit the nebulization of some formulations. Advances in pulmonary drug delivery technology have led to the development of nebulizers that improve delivery efficiency and reduce drug wastage [26, 33, 34].

Intratracheal Instillation

By this technique, a small amount of drug solution is instilled into the lungs by syringe. The deposition of the drug is localized and uneven and only a small absorptive area is used for absorption from the deposition. Intratracheal instillation provides a route of rapid and quantifiable delivery of drugs to the lungs [35].

PARENTERAL

To achieve the desired pharmacological action of a drug, it has to reach the site where it will exert its action. This translocation of drug from site of action to the site of administration depends highly upon the route by which it is administered [36]. The parenteral route i.e. administration by injection is the fastest and the most certain route of administration [37]. The term parenteral is made up of two word- *par* meaning beyond and *enteral* meaning intestine. Hence, we can say that parenteral administration is drug delivery by injection which transports the drug directly to the body fluid or blood escaping the intestinal mucosa route. Thus, this route overcomes the limitation of the oral route [3].

Advantages [38]

- [1] Drugs that have poor absorption in the GIT and drugs like insulin which are unstable in the GIT track can easily be administered by this route.
- [2] It is one route that allows control over the dose to be administered.
- [3] It is the most reliable route in case of emergencies as the administration of the drug is faster leading to a more efficient action.
- [4] No side effects of gastric irritation and vomiting occur.
- [5] The limitation of having the medicine on an empty or a full stomach is avoided as digestive juices or food doesn't pose any interference.
- [6] Interference by liver metabolism is avoided.
- [7] Unconscious, uncooperative and vomiting patients can be easily dealt with.

Disadvantages [3]

- [1] The entire preparation equipments have to be sterilized along with the final preparation.
- [2] With reference to the above point, it is evidently costlier.
- [3] Help is always needed to administer a parenteral dosage form.
- [4] It is an invasive and painful technique.
- [5] It poses more risks than the other routes.
- [6] There are higher chances of injury to the local tissue.

Classification of Various Types of Parenteral Routes

The various parenteral routes can be classified on the basis of site of action as follows [36, 3].

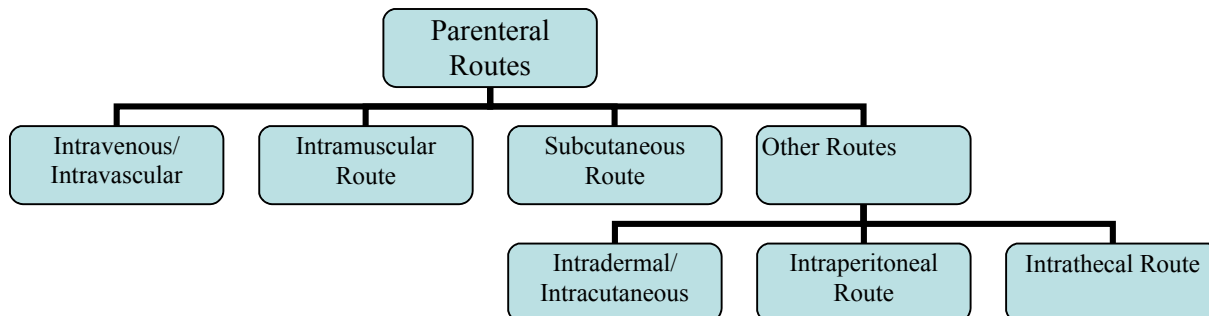


Fig. 2

Fate of Drug in Body After Parenteral Administration

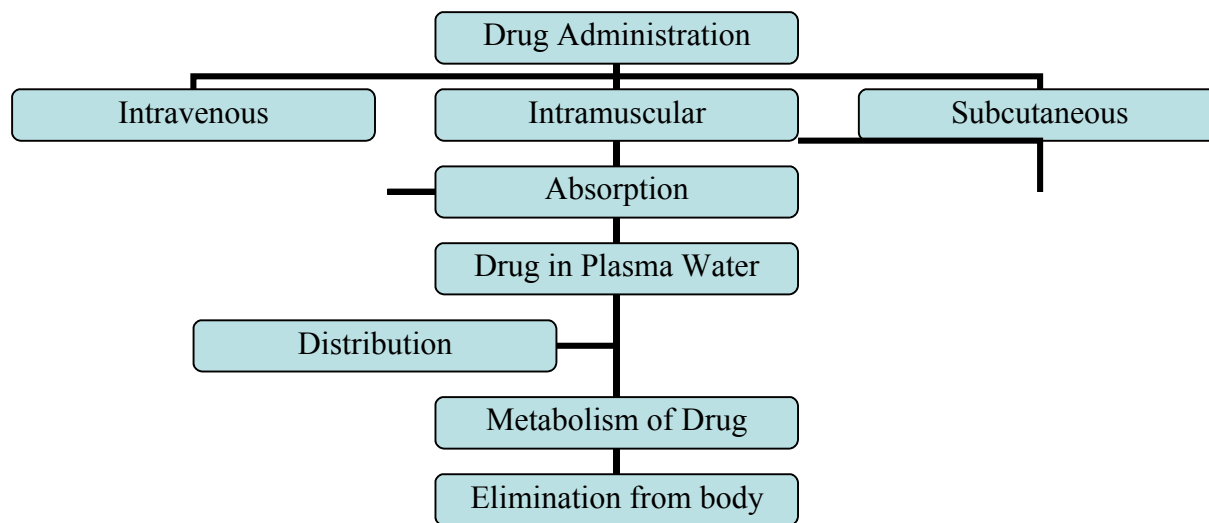


Fig.3

Intravenous Route

The drug is injected in the vein lumen, primarily the antecubital vein [36] (superficial veins) in the form of a bolus or as an infusion [3]. The bolus injection results in a very high concentration of drug initially in the right chambers of the heart and then lungs. Then this high concentration reaches the systemic circulation. However, in this case, the peak concentration reached by the administered drug depends highly on the rate at which the drug is injected. The i.v. infusion is a better method than the bolus administration as it avoids the a) vagueness in absorption of the drug from other sites and b) the high plasma concentration that occurs due to a bolus injection [37]. It is the most widespread mode of administration [38].

Advantages [3, 36, 38]

- [1] Drug reaches the stream of blood immediately having full access to the entire body and hence, rapid action is produced rendering this route to be the most efficient in emergencies.
- [2] Drugs causing even high intensity of irritation can be administered as the vein intima is insensitive and hence, the blood dilutes the drug moiety.

- [3] Drug dose titration is possible in a situation where the drug has a short duration of action and the response can be measured precisely.
- [4] Very small dose is required.
- [5] Bioavailability is 100%.
- [6] Very large volume infusions of the drug can be given.
- [7] The drug bypasses first pass metabolism.
- [8] Hypertonic solutions can also be administered along with GIT irritation causing drugs.
- [9] Drugs can be delivered at a uniform rate.

Disadvantages [3, 36, 38]

- [1] If the drug administration accompanies extravasation, then thrombophlebitis and venous thrombosis of the vein in which drug is injected and necrosis of the tissues surrounding that particular vein can occur.
- [2] As the vital organs of the body like heart and lungs get exposed to a high drug concentration, thus, this route has the maximum risk factors.
- [3] Only aqueous solutions of the drug can be administered. Suspensions can't be administered.
- [4] Depot preparations i.e. oily solutions and aqueous suspensions of this route can't be made.
- [5] Another factor that makes this route risky is that once the drug has been administered, it can't be removed by various methods like forced emesis or binding of charcoal (activated) as introduction of any particulate matter or any other substance can lead to fatal embolism.
- [6] This route has a high probability of bacterial contamination.
- [7] IV injection may induce hemolysis and other similar conditions if the drug is administered too rapidly.

The **examples** of drugs that are given through this route are Propofol (an anesthetic), Diazepam (for treatment of status epilepticus) [37], Glucose, Saline Glucose and many antibiotics [36].

Intramuscular Route

There are several sites of injection- large muscles like the deltoid, triceps, gluteus maximus, rectus femoris [3].

Advantages [3, 38]

- [1] As the muscles have less sensory nerves terminating in them, so drugs that cause mild irritation can be injected.
- [2] This method causes less pain than the i.v. method.
- [3] Absorption is faster as the muscular area is vascular.
- [4] Unlike the i.v. preparations, depot preparations (e.g. a suspension of the drug made in a vehicle which is non-aqueous like PEG, of this route can be made and hence, sustained drug effects can be achieved.

Depot preparations i.e. suspensions for the intramuscular route in non aqueous vehicles give a sustained release effect by the following process: precipitation of the drug takes place at the site of injection when the vehicle diffuses out of the muscle. This precipitated drug is dissolved slowly thereby, giving a constant drug dose over a long period of time. Haloperidol works by this mechanism imparting a neuroleptic effect [38]. Depot injection of testosterone and perphenazine (again for neuroleptic action) also works by this mechanism. Other examples of drugs administered by this method are several anti-emetic and antibiotics [36].

Disadvantages [3, 36]

- [1] Assistance is always required as the drug is to be injected deep in the muscle.
- [2] Local hematoma can occur in patients taking anticoagulant drugs; hence, care should be taken before an i.m. injection.
- [3] An abscession can occur at the site of injection.
- [4] Unlike i.v., large volumes can't be administered.
- [5] There are chances of damage to the nerve leading to paresis of the muscle that the nerve supplies.
- [6] Site complications.

Subcutaneous Route

Both the subcutaneous and intramuscular routes are faster than the oral route. But, they pose a limitation as the rate of absorption to an extent depends upon the site where the drug is administered and the local flow of blood on this site. The rate limiting factors for the absorption of the drug are:

- a) Diffusion of the drug throughout the tissue.
- b) Drug removal by the local flow of blood.

Point a) is proved by the example of the enzyme hyaluronidase which breaks the intercellular matrix leading to an increase in the process of diffusion. Thus, it leads to an increase in the absorption of the drug. Also, considering b), we can conclude that an increase rate in flow of blood increases the absorption while patients suffering from shock i.e. circulatory failure exhibit slower absorption of the drug [37]. This happens because patients suffering from shock have reduced peripheral circulation [36] and vasoconstriction in their vessels leading to delayed absorption [3]. The site of action for this route is the loose subcutaneous tissue under the skin [36, 3].

Advantages

- [1] Minimized risk as compared to i.v. [38]
- [2] No assistance is needed as the injection need not be penetrated deeply [3].
- [3] Depot preparations for sustained action can be made [3].
- [4] Smooth absorption over a long period of time [37].

Disadvantages [3, 36]

1. As the tissue is less vascular, slower rate of drug absorption is there as compared to intravenous and intramuscular route.
2. The site of injection is richly supplied with nerves hence, drugs causing irritation can't be administered by this route because it may result in sloughing and necrosis.
3. Similar to the i.m. route, only small volumes can be administered.

Special forms of subcutaneous route:

a) *Dermojet*: This method is used sans a needle. In this method, the drug is projected from an extremely small pore using a gun like instrument. This projection of the drug is done at a very high velocity and so the drug passes through the various layers and finally, gets deposited in the subcutaneous tissue. It is a painless method and is beneficial for mass inoculations.

b) *Implantation of pellets*: The drug is incorporated in form of solid pellets and is placed under the skin for sustained release over a long period of time.

c) *Nonbiodegradable and biodegradable implants*: Here, the crystalline drug is incorporated in tubes or capsules and planted under the skin like the pellets. The nonbiodegradable ones have to be removed after some time but biodegradable implants don't pose this problem [3].

The **examples** of drugs administered via this route are- the oral contraceptive levonorgestrel incorporated in silastic capsules for longer duration of action, insulin incorporated in mechanical pumps [38], local anesthetics and vaccines which are preferred by this route as the active protein moiety directly reaches the lymphoid tissues through the lymphatics without any interference from any other enzyme [36].

Comparison of the Intramuscular, Intravenous & Subcutaneous Routes [3, 36-38]

Feature	Intramuscular Route (i.m.)	Intravenous Route (i.v.)	Subcutaneous Route (s.c.)
1. Site of administration	Large muscles like deltoid, triceps	In the vein lumen	Loose subcutaneous tissue under the skin
2. Depot Preparations	Can be made	Can't be made	Can be made
3. Absorption Rate of drugs	In between i.v. and s.c.	Highest	Slowest
4. Drug Volume that can be administered.	Small volumes	Large volumes	Small volumes
5. Assistance	Required	Required	Not Required
6. Irritant Drugs	Mild irritation causing drugs can be given	Can be given	Can't be given
7. Risk Frequency	Lower than Intravenous route	High	Low

Table 1: Comparison of the i.m., i.v. and the s.c. routes

Other Routes

1. Intradermal Route

This route involves the scarring or multiple puncturing of the epidermis through a drug drop to administer the drug into the epidermis. The drug is given in small doses via a tuberculin syringe and the absorption rate is slow. The various examples are BCG vaccines, sensitivity and diagnostic tests [3].

2. Intraperitoneal Route

The injection is given in the peritoneal space leading to a high absorption rate credited to the available large surface area. This route may cause infections in the peritoneal cavity and is painful and risky. Antirabies drugs are given by this route along with drugs used for treatment of poisoning and renal failure. This is the most common method used for the administration of drugs to animals used in the lab [36].

3. Intrathecal Route

This route involves the injection of the drug into the sub arachnoid space i.e. the cerebrospinal fluid (CSF) through a lumbar puncture needle [37].

This route offers the advantage of high availability of the drug in the CSF as the blood brain barrier and blood- CSF barrier is by passed. Hence, the drug acts directly on the CNS.

However, this injection requires great skill and extreme sterile conditions. Also, it is a painful and risky procedure.

Various drugs given by this route are xylocaine injection for anesthesia of the spine, radiopaque media for visualization of the spinal cord [36], methotrexate for leukemia treatment to prevent CNS relapse, bupivacaine for regional anesthesia, baclofen for muscle spasm treatment. Certain antibiotics, that are necessary in extreme conditions but are unable to cross the blood brain barrier, can be administered via this route [37].

Recent Advances in Parenteral Drug Delivery

There are many drug delivery systems that have emerged as newer technologies for parenteral drug delivery. These systems include microspheres, liposomes, niosomes, solid-lipid nanoparticles (SLN's) and pharmacosomes besides others [39].

1. Microspheres

They are microparticles consisting of a solid lipophilic fat core surrounded by a monolayer of phospholipids [40]. Previously, only a peptide solution/suspension was administered intravenously, intramuscularly or subcutaneously. However, the frequency of administration was high; this approach required surgical implants which caused discomfort and fluctuations in plasma level of the drug occurred. So, to develop a controlled release parenteral dosage form, peptides were entrapped in implants and used. A newer alternative that emerged was polymers that were dissolved in a biocompatible organic solvent with the drug dispersed in the polymeric solution [41]. Both biodegradable and non biodegradable were been investigated and the result shows that in case of parenteral delivery, non biodegradable polymers as carriers remaining in the body after drug release pose toxicity threats. Biodegradable polymers don't show this threat. The main advantage of microspheres is that they can be injected into the body with a hypodermic needle but this also becomes a drawback as once injected, they can't be completely removed from the body in case of an adverse reaction. Parenteral administration of microspheres requires sterility and their incorporation into a suitable vehicle for injection. It leads to complete absorption of the drug [42]. It is also preferred over the nasal, vaginal, oral and topical routes as they have an inherent physical and chemical instability and biological short half-lives [41]. Hydrophilic molecules can easily be dispersed in aqueous medium while hydrophobic microspheres are not able to do so. This is where microspheres lag behind other vesicular carrier systems as they are not amphiphilic [42].

2. Liposomes

They are microscopic structures that contain an aqueous volume which is enclosed by a lipid membrane [43]. They basically consist of one or more lipid bilayers which are concentric and separated by aqueous compartments [40]. The drug is present either in the aqueous compartment or in the lipid bilayers. This drug position depends upon the physico-chemical properties of the drug and the characteristics of the lipids. The main components of the liposomes are phospholipids and cholesterol. Liposomes perform similar functions as compared to controlled drug delivery systems but the release of drug is much faster. Another difference is that they can alter the distribution pattern of the drug in the body. There may be interaction of the liposome with the cells of the body leading to a stage where drug release doesn't occur and the drug and the carrier are taken up by the cells. A major problem associated with liposomal drug delivery is stability. Liposomes are prone to both physical and chemical degradation. However, factors like cell liposome interaction, a localized drug effect, enhanced uptake of drug and structural flexibility impart liposomes desired characteristics of a suitable drug delivery system. They are used in drug delivery of chemotherapeutic drugs and vaccines [43].

3. Niosomes

They are non ionic surfactant vesicles which can trap both hydrophilic and lipophilic drugs owing to the presence of an aqueous layer and lipid membrane. Non ionic surfactants like Tweens and Spans are used with cholesterol to entrap the drug. They are better than liposomes in terms of stability and a better release and targeting of drugs to tumor, liver and brain is achieved due to the non ionic surfactant. Apart from liposomes, this also makes them superior to microspheres and nanoparticles. They further offer the advantages that they require no special conditions for their handling and storage, they achieve better bioavailability with lesser side effects, they are non toxic and biodegradable and they attain a higher therapeutic index of the drug by limiting its release to the targeted organ only. The major disadvantage is chemical instability because the phospholipids undergo oxidative degradation. Also, they may interact with serum components leading to removal of the lipid layer and leakage of the entrapped drug. They also tend to fuse with each other on long time standing leading to an obstacle in their manufacturing process. They have been used as drug carriers for anti cancer, anti infective and anti- AIDS drugs. Anti cancer targeting is specifically of importance as niosomes can be transported easily to macrophages which infiltrate the tumor cells. These activated macrophage systems can be used to deliver anti cancer agents more quantitatively to the tumors [44].

4. Solid- Lipid Nanoparticles

They are a new type of colloidal drug delivery system for intravenous administration. They consist of solid lipid nanoparticles dispersed in an aqueous surfactant. Their structure consists of a solid lipid core in which the drug is dissolved surrounded by hydrophobic chains of phospholipids arranged in a monolayer. They can be used effectively for administration of poorly water-soluble drugs. They have the advantage that they show no residues from organic solvent and low cardio and systemic toxicity and are biocompatible. They are also suitable candidates for sustained drug delivery as multiple, warm microemulsions can be prepared. Ease of large scale production, unlike polymer nanoparticles and sterilization contribute to the manufacture of their parenteral formulations. They combine the advantages of fat emulsions, polymeric nanoparticles and liposomes and avoid their disadvantages. Their main advantage over other vesicular systems is that they don't manifest the problems of aggregation and drug leakage. Low cost of ingredients, ease of preparation and high entrapment are other advantages [45].

5. Pharmacosomes

They are also colloidal dispersions of drugs that are bound to lipids in a covalent manner. They are called so as the drug delivery system is formed by joining a drug (pharmakon) to a carrier system (soma). They can be present in the form of ultrafine vesicular, micellar or hexagonal aggregates. Their major advantage over other vesicular drug delivery carriers is that they are pure drug vesicles which are formed by amphiphilic drugs. Any drug possessing an active hydrogen moiety like –COOH or -OH can be esterified to the lipid and its synthesis can be guided in such a way that results in the development of an amphiphilic compound. They are also superior to classical vesicular drug delivery systems as

- a) They don't require the tedious step for removal of the free, untrapped drug from the final formulation.
- b) Also, the interaction between drug-lipid and volume of drug encapsulated don't influence entrapment efficiency. Entrapment efficiency is high and predetermined.
- c) Membrane fluidity of liposomes is influenced by the lipid composition. But, covalent bonding of the drug in pharmacosomes offers the advantage that the rate release is not affected as the membrane fluidity is dependent upon the phase transition temperature instead of lipid composition.
- d) Drug leakage does not take place as the drug is covalently linked.
- e) Drug can be incorporated without problem.

Similar to niosomes and liposomes, pharmacosomes also present an efficient system for targeted drug delivery with less toxicity and reduced cost because of higher bioavailability. However, they pose the problem of drug loss through hydrolysis. They also undergo chemical degradation and fusion and aggregation. They have been used successfully to improve the therapeutic performance of drugs like bupranolol hydrochloride, acyclovir and pindolol maleate. Other than being given intravascularly, pharmacosomes can be given orally, topically or extra-vascularly too [40].

Comparison of the Various Vesicular Carrier Systems

TYPES	Size Range	Systemic and Cyto-toxicity	Sustained Release	Drug Leakage and aggregation	Amphiphilic Nature	Chemical stability
Microspheres	0.2-100 μm	Low	Yes	Yes	No	High
Liposomes	25nm-100μm	Low	No	Yes	Yes	Low
Niosomes	10-1000 nm	Low	Yes	Yes	Yes	Low
SLN's	10-1000 nm	Low	Yes	No	Yes	High
Pharmacosomes	-	Low	Yes	Yes	Yes	Low

Table 2: Comparison of the various features of microspheres, liposomes, niosomes, SLN's and pharmacosomes

Nanosuspensions for Parenteral Drug Delivery

The need for nanosuspension as parenteral drug delivery was recognized for administration of therapeutic concentrations of the water insoluble dosage forms. Nanosuspensions were suitable formulations as no solvents were needed, intravenous delivery was aided due to the small particulate size and high loading was possible due to the solid crystal phase. This inherent high loading differentiates nanosuspensions from liposomes, emulsions and polymeric nanoparticles. They can be administered by the following parenteral routes-subcutaneous, intravenous, intradermal, intramuscular and intrathecal. They offer higher advantage over the conventional drugs by similar routes because there is elimination of noxious excipients leading to decreased systemic toxicity. Safety profile of injectable nanosuspensions was studied from the following two perspectives:

1. Vessel occlusion as a function of size and number of the particles.
2. Response of the monocyte phagocytic system

It was inferred that particles having a size of less than 40 micrometers and a sufficiently low particle load resulted in efficient nanosuspensions. Also, it was concluded that these suspensions put lesser load on the macrophages as compared to inert particles as they are processes at a much faster rate than the phagolysosomes.

These nanosuspensions have been used in treatment of regional anesthesia, malignant hyperthermia and as an anticancer formulation (paclitaxel) [46].

CONCLUSION

In the current scenario, Transdermal, Pulmonary and Parenteral are the leading routes of drug administration, other than the most common route- the Oral route. They help overcome the bioavailability and absorption problems associated with the Oral route. Thus, the efficacy of the therapy increases. Transdermal medication delivers a steady infusion of drug over a prolonged period of time, thereby providing controlled drug delivery and increasing patient compliance. When the drug is administered parenterally or in the form of transdermal patches, it is not subjected much to first pass metabolism and hence the bioavailability of the drug is more. Pulmonary dosage forms and transdermal drug delivery systems are convenient to use. They can deliver the medication directly to the affected area. Further, parenteral route is the route of choice in case of emergencies. The novel approaches in drug delivery help to target the drug to the site of action, which decreases the peripheral adverse effects. Such approaches include microspheres, vesicular systems and nanoparticles, among others.

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