

Chapter 2

Routes of Drug Administration

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PH1.3: Enumerate and identify drug formulations and drug delivery systems.

PH1.11: Describe various routes of drug administration, e.g., oral, SC, IV, IM, SL.

Learning Objectives

- Local route.
- Systemic route.

Introduction

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.

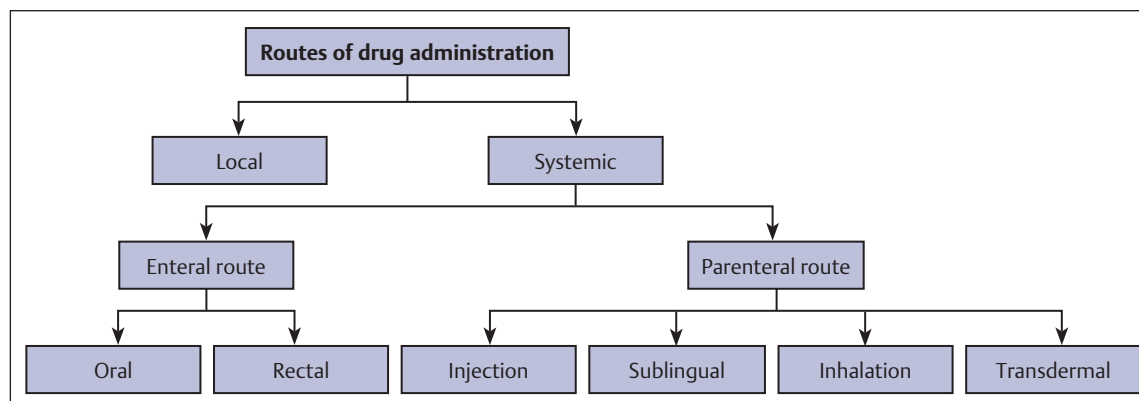


Fig. 2.1 Routes of drug administration.

- Suppository solid dosage form drug is inserted in rectum, for example, bisacodyl for bowel evacuation.
- Eye, ear, and nose—Drugs can be delivered to nasal mucosa, eyes, or ear canal in the form of drops, ointments, and sprays. This route can be employed for allergic/infective conditions of these organs.
- Bronchi (inhalational)—This route of drug administration is used for conditions like bronchial asthma and chronic obstructive pulmonary disorder (COPD), wherein drug is absorbed by bronchial mucosa through inhalation, for example, salbutamol.
- Vagina—Drugs can be applied/inserted in the form of tablet, cream, or pessary to vagina. This route is mainly used for vaginal candidiasis.
- Urethra—Medication in the form of solution/jellies can be applied to urethra, for example, lignocaine.

Deeper Areas

These are, for example, intra-articular tissue or retrobulbar region. They can be reached by using syringe and needle. However, in order to reduce systemic absorption of drug, only slowly absorbed drugs should be used, for example, lidocaine for local anesthesia can be given as intrathecal injection. Also, hydrocortisone acetate is given as an intra-articular injection.

Systemic Route

Through this route, drug reaches the blood, is distributed across the body, and produces systemic effects. Broadly, this route can be divided into enteral, parenteral, and specialized drug delivery.

Enteral Route

This route includes oral and rectal.

Oral

This is the most common and accepted route of drug administration. Following oral administration, drug reaches the systemic circulation and is widely distributed across all tissues. Oral route has advantages of being safe, painless, and convenient for repeat and long-term use. Moreover, through this route, drug can be self-administered and does not require professional assistance. However, oral route has few limitations like slow onset of action, and thus cannot be given in emergencies, unpalatable/irritant drugs (e.g., chloramphenicol), unabsorbable drugs (e.g., neomycin), drugs with high first-pass metabolism (e.g., lignocaine), medications destroyed by digestive juices (e.g., insulin). Other drawbacks included are they cannot be given in unconscious/uncooperative/unreliable patients and those having vomiting and diarrhea. Many dosage forms are available for oral administration; for example, solid forms like tablets, capsules, and liquid preparations such as syrups, elixirs, and suspensions. Tablets are made by compressing powdered drug along with binding agents and excipients, whereas capsules contain shell of gelatin, which is a tasteless natural substance. Two types of capsules are available—hard gelatin capsule (contain drug in solid form) and soft gelatin capsule

(drug as an oily liquid form). In case of pediatric patients, swallowing of tablets/capsules is often problematic; in such cases, oral liquid preparations can be used.

Some of the abovementioned limitations of this route can be overcome by enteric coating of tablets and/or sustained/controlled release formulation. Enteric coating of tablets is done by cellulose and acetate. This has advantages like it prevents gastric irritation, protects drug from gastric acid, and retards drug absorption, thus increasing its duration of action. On the other hand, sustained/controlled release formulations have different coatings which dissolve at different time intervals. Advantages of this formulation are increase in duration of action, thus decreasing dosing frequency and increasing patient compliance, for example, sustained release nifedipine.

Sublingual

Drug which is lipid soluble is kept under the tongue or crushed and applied to buccal mucosa. Drug is absorbed into veins surrounding oral mucosa; later, it enters superior vena cava and heart and eventually reaches systemic circulation, for example, buprenorphine and nitroglycerin (used to terminate anginal attack). Advantages of this route is that drugs with high first-pass liver metabolism are readily available in systemic circulation when given by this route. Other advantages include rapid onset of action, drug can be self-administered, and action can be terminated by spitting out tablet. Limitations of this route is that it is irritant, lipid insoluble, and unpalatable; hence, it cannot be given. Additionally, it cannot be used in children.

Rectal

This route can be used for systemic effects apart from local effects. Drugs are absorbed by hemorrhoidal veins, and to some extent, they bypass liver metabolism. This route possesses certain advantages like irritant/unpleasant drug can be administered through this route. It can be used as suppository as well as in uncooperative/recurrent vomiting patients. Nevertheless, it has limitations like being embarrassing to patients, having erratic drug absorption, and leading to rectal inflammation in case of irritant drugs, for example, diazepam for febrile convulsions in children.

Parenteral Route (IM1.30)

This is route of drug administration other than the enteral route. It includes drugs administered by injection, inhalation, and transdermal route. It has advantages like rapid onset, thus can be used in emergency; also, it can be used in uncooperative patients and patients with vomiting/diarrhea. This route is suitable for irritant drugs, drugs with high first-pass metabolism, orally nonabsorbable drugs, and medication destroyed by digestive juices. Disadvantages of this route are that it is expensive and not easy for self-administration.

Inhalation

Volatile liquids and gases are administered by this route, for example, general anesthetics. Inhaled drug is absorbed through vast surface of alveoli; hence action is rapid.

Moreover, when drug administration is stopped, remaining drug in alveoli will be expelled quickly. Hence, termination of drug action as well as moment-to-moment drug regulation can be achieved through this route. However, irritant drugs can cause increased respiratory secretion and bronchospasm.

Transdermal Route (Adhesive Patches)

Patches deliver drug into circulation for systemic effects. Patches have multilayers like backing film, drug reservoir, rate controlling micropore membrane, and adhesive layer with priming dose, for example, scopolamine for motion sickness, nitroglycerin for angina, estrogen for hormone replacement therapy (HRT), and fentanyl for analgesia. Few advantages of this route include self-administration, good-patient compliance, prolonged action, minimal side effects, and constant plasma concentrations of drug. However, this route has drawbacks like being expensive, local irritation (itching, dermatitis), and patch may fall without being noticed.

Injection (Fig. 2.2)

Intradermal

Drug is injected into dermal layer of skin, for example, bacillus Calmette–Guerin (BCG) vaccination and drug sensitivity testing.

Subcutaneous (SC)

Drug is injected into SC tissue which has nerve supply but less vascular supply, for example, insulin and adrenaline. Self-administration is also possible; depot preparations for prolonged action can be used, for example, norplant for contraception. This route is unsuitable for irritant drugs as well as has slow onset, thus cannot be used in emergency.

Intramuscular (IM)

Drug is injected into large muscles, deltoid, gluteus maximum, and lateral aspect of thigh in children. With this route, rapid onset of action can be achieved compared to oral route; also, depot preparations (used to prolong drug action), mild irritants, soluble substances, and suspensions can be given. Nonetheless, IM route requires aseptic condition,

administration by professionals, can be painful, and may lead to abscess and local tissue injury.

Intravenous (IV)

Direct injection of drug into vein. Drug can be given as bolus administration as well as slow IV infusion. Bolus administration is single, large dose rapidly/slowly injected as single unit, for example, furosemide, whereas slow IV injection involves addition of drug into a bottle containing dextrose/saline, for example, dopamine infusion in cardiogenic shock. With this route, 100% bioavailability and rapid onset of action can be achieved; hence it is suitable for emergencies. For example, when sedative drug midazolam is IV administered, sedation occurs in 2 to 4 minutes. Moreover, large volumes of fluids, for example, dextrose and highly irritant drugs, for example, anticancer drugs can be given through this route. Constant plasma concentration can be maintained using this route of administration. However, once drug is injected, drug action cannot be terminated. Administration of drug through this route can cause local irritation, thrombophlebitis, and necrosis.

Requirement of strict aseptic conditions and impossibility of self-administration are its other drawbacks. Also, depot preparations cannot be given. Caution in the form of ensuring tip of needle is in vein as well as slow administration of drug should be exercised while giving drugs through IV route.

Intra-arterial

This route is used when localized effect of a drug in a particular tissue or organ is desired. For example, in the treatment of renal tumor or head/neck cancer, drug is injected into renal artery or carotid artery, respectively.

Intrathecal

Injection of drug into subarachnoid space (into cerebrospinal fluid [CSF]). This route can be used as a method for direct delivery of a drug into central nervous system (CNS), for example, spinal anesthesia (lignocaine) and antibiotics (in meningitis).

Epidural Injection

This is injection into epidural space, which is area outside dura mater. It is different from intrathecal as drug is not

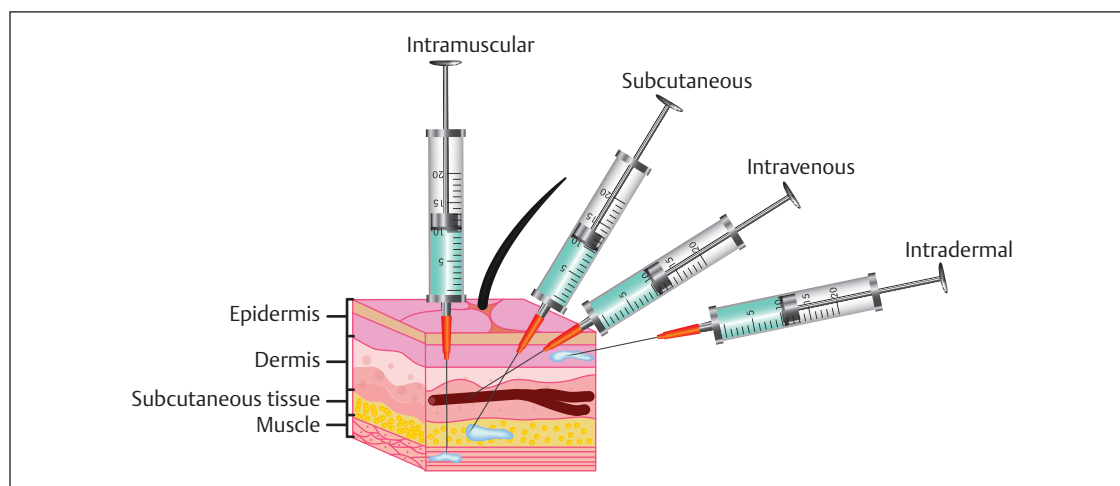


Fig. 2.2 Types of injection.

directly administered into CSF. Local anesthetic drugs are given by this route to provide analgesia during childbirth.

Intra-articular

Drug is injected into joint space, for example, hydrocortisone for rheumatoid arthritis. This route requires aseptic condition and can cause damage to cartilage on repeated use.

Specialized Drug Delivery (PH1.3)

Ocusert

Drug is kept beneath lower eyelid, for example, pilocarpine in glaucoma. Major advantage is single application releases drug for 1 week.

Progestasert

It is intrauterine contraceptive device which releases progesterone for 1 year.

Liposomes

Drug incorporated in minute phospholipid vesicles, for example, liposomal amphotericin for fungal infection.

Monoclonal Antibiotics

These are immunoglobulins which react with specific antigen. These can be used for targeted delivery, for example, anticancer drugs.

Multiple Choice Questions

1. Drug administered through the following route is most likely to be subjected to first-pass metabolism:

- A. Oral.
- B. Sublingual.
- C. Subcutaneous.
- D. Rectal.

Answer: A

Total drug absorbed orally is subjected to first-pass metabolism in the intestinal wall and liver, while approximately half of that absorbed from the rectum passes through the liver. Drug entering from any systemic route is exposed to first-pass metabolism in the lungs, but its extent is minor for most drugs.

2. Transdermal drug delivery systems offer the following advantages, except:

- A. They produce high peak plasma concentration of the drug.
- B. They produce smooth and nonfluctuating plasma concentration of the drug.
- C. They minimize interindividual variations in the achieved plasma drug concentration.
- D. They avoid hepatic first-pass metabolism of the drug.

Answer: A

The micropore membrane is such that the rate of drug delivery to skin surface is less than the slowest rate of absorption from the skin. As such, the drug is delivered at a constant and predictable rate irrespective of site of application. They provide smooth plasma concentrations of the drug without fluctuations.

3. In addition to slow intravenous infusion, which of the following routes of administration allows for titration of the dose of a drug with the response?

- A. Sublingual.
- B. Transdermal.
- C. Inhalational.
- D. Nasal insufflation.

Answer: C

When administration is discontinued, the drug diffuses back and is rapidly eliminated in the expired air. Thus, controlled administration is possible with moment-to-moment adjustment.

4. Which of the following drugs is administered by intranasal spray/application for systemic action?

- A. Phenylephrine.
- B. Desmopressin.
- C. Azelastine.
- D. Beclomethasone dipropionate.

Answer: B

Certain drugs, such as GnRH agonists and desmopressin applied as a spray or nebulized solution, have been used by this route. Desmopressin is the preparation of choice for all V2 receptor-related indications. The intranasal route is preferred.

5. Compared to subcutaneous injection, the intramuscular injection of drugs:

- A. Is more painful.
- B. Produces faster response.
- C. Is unsuitable for depot preparations.
- D. Carries greater risk of anaphylactic reaction.

Answer: B

The muscle is more vascular (absorption of drugs in aqueous solution is faster).

6. Select the route of administration that carries the highest risk of adversely affecting vital functions:

- A. Intra-arterial injection.
- B. Intrathecal injection.
- C. Intravenous injection.
- D. Intramuscular injection.

Answer: C

This is the most risky route, as vital organs such as heart and brain get exposed to high concentrations of the drug.