Review Article

Delivery strategies and human routes of administration: a review

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Abstract

One significant non-invasive method for delivering medicinal drugs both locally and systemically is the vaginal route. The vaginal route provides improved bioavailability for numerous medications due to its abundant vascularization, broad absorptive surface, and avoidance of first-pass metabolism. It is frequently used to treat hormone control, infections, contraception, and reproductive health. While sophisticated methods including mucoadhesive formulations, vaginal rings, nanoparticles, and in-situ gelling systems offer better retention, controlled release, and patient compliance, conventional dose forms include creams, gels, suppositories, and pills. While this approach has benefits including sustained delivery, ease of administration, and few systemic side effects, it also has drawbacks, such as absorption fluctuation becauseto hormonal and menstrual cycle fluctuations, leakage or messiness in semi-solid formulations, and possible excipient irritation. Therapeutic results may also be impacted by limitations in patient acceptance and dosage volume. Vaginal pH, epithelium thickness, microbiota, medication qualities, and formulation features are all factors that affect vaginal absorption. All things considered, vaginal medication delivery is still a flexible and developing discipline, with new technologies improving comfort, efficiency, and targeting for a variety of systemic and gynecological treatments.

Keywords: Vaginal, Non-invasive method, Delivery strategies, Gynecological treatment, Routes of administration.

Introduction

The effectiveness with which the active pharmaceutical ingredient (API) reaches its target site of action in the body is a major factor in the success of any therapeutic intervention. The pharmacokinetics, pharmacodynamics, effectiveness, and safety profile of therapeutic medicines are all significantly influenced by drug delivery methods and administration routes. The drug's bioavailability, patient compliance, therapeutic results, and frequency of administration are all impacted by the delivery method selection[1].The design and development of methods or formulations that regulate the pace, duration, and location of medication release in the body are referred to as drug delivery techniques. Conventional dosage forms, such tablets and injections, frequently have drawbacks including low solubility, quick drug degradation, or non-specific distribution, which can result in side effects or less than ideal therapeutic results. Parenteral routes—intravenous, intramuscular, and subcutaneous—allow medications to reach the systemic circulation directly, providing quick start of action and exact dosage management, but they frequently call for sterile preparations and skilled staff. For local or systemic effects, topical and transdermal methods offer non-invasive delivery with the possibility for prolonged release. The capacity of the pulmonary, nasal, ocular, and vaginal routes to transfer macromolecules such peptides, proteins, and nucleic acids without causing gastrointestinal breakdown has drawn attention. Nanotechnology, biodegradable polymers, and intelligent responsive systems that can adjust to physiological circumstances or stimuli like pH, temperature, or enzymes are becoming more and more important components of modern delivery tactics. The physicochemical characteristics of the medication, the intended therapeutic impact, the patient's condition, and the length of the treatment all play a role in choosing the best route and delivery method. By ensuring that the medication reaches its target site at therapeutic concentrations for the necessary amount of time, an ideal delivery strategy reduces side effects and increases compliance[2].

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❖ Oral Delivery

Because of its ease of use, affordability, and high patient compliance, oral delivery is the most popular and favoured method of administering medications. It entails taking a medication formulation orally and then absorbing it through the gastrointestinal (GI) system. Despite its extensive usage, oral administration poses serious problems because of limited permeability across intestinal epithelium and breakdown in the hostile GI environment, especially for macromolecules like peptides, proteins, and nucleic acids.

Mechanism and Pathway

Oral medications go through a number of steps after consumption, including disintegration, dissolution, absorption, metabolism, and systemic distribution. The small intestine is the primary route of absorption for the majority of medications due to its enormous surface area and abundant blood flow. While hydrophilic or bigger molecules may need carrier-mediated or endocytic processes, lipophilic and tiny molecular medicines are usually absorbed through passive diffusion[3,4].

Strategies to Enhance Oral Bioavailability

Several formulation and delivery techniques have been developed to get around these obstacles. Nanocarriers and Encapsulation Polymeric micelles, liposomes, and nanoparticles improve the drug's permeability across mucosal layers and shield it against deterioration. For example, the stability and absorption of peptides

and bacteriophages have been enhanced by the use of chitosan and PLGA nanoparticles. Because of its ease of use, non-invasiveness, affordability, and high patient compliance, oral delivery is the most popular and favoured method of administering medications. Oral use accounts for between 60 and 70 percent of all pharmacological formulations on the market. Oral distribution presents a number of difficulties with medication solubility, stability, and bioavailability despite its benefits, especially for macromolecules including peptides, proteins, and nucleic acids.

Advantages of Oral Delivery

1. Administration Ease: Oral formulations are easy to use and don't require medical monitoring.

2.Patient Compliance: Non-invasive nature increases adherence, especially in chronic therapy.

3. Cost-Effectiveness: Compared to parenteral methods, manufacturing and storage are simpler.

4. Safety: Compared to injectable approaches, there is less chance of harm or infection.

Challenges in Oral Delivery

1. Enzymatic Degradation: Before being absorbed, sensitive medications like proteins and peptides are broken down by proteolytic enzymes found in the gastrointestinal (GI) tract, such as pepsin, trypsin, and chymotrypsin.

2. Poor Permeability: The intestinal epithelium is difficult for large or hydrophilic molecules to pass through.

3. Low Solubility: Inadequate absorption results from the poor water solubility of several medications.

4. First-Pass Metabolism: The liver extensively metabolises drugs, which lowers their systemic availability.

Strategies to Enhance Oral Bioavailability

A number of formulation techniques have been developed to address the difficulties associated with oral delivery.

1. Nanoparticle Systems: Solid lipid nanoparticles, liposomes, and polymeric nanoparticles increase solubility and shield medications from deterioration.

2. Use of Permeation Enhancers: Intestinal permeability is increased by substances such as fatty acids, bile salts, and surfactants.

3. Mucoadhesive Systems: Drugs stay at the absorption site longer thanks to polymers like chitosan.

4. Prodrug Approach: Chemically altering medications to increase their permeability and stability.

5. Enteric Coating: Releases medications in the intestine and shields them from the breakdown of gastric acid.

6. Self-emulsifying Drug Delivery Systems (SEDDS): Improves lipophilic drug solubility.

- **Intravenous (IV) Route**

❖ **Parenteral routes**

By injecting medication, the parenteral method avoids the gastrointestinal system. It enables quick action, 100% bioavailability, and exact dosing.

Fig no. (1) Intravenous route

When a drug is injected straight into a vein, it enters the bloodstream right away[4].

Advantages

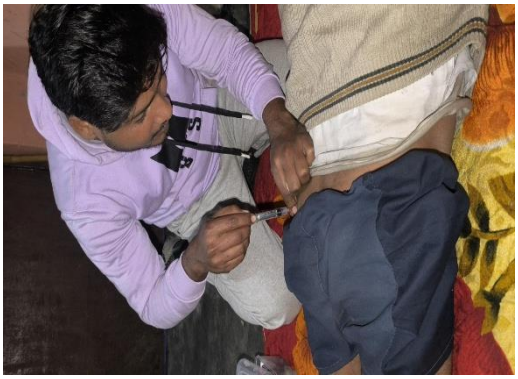
Quickest rate of activity
Complete bioavailability
Appropriate for emergency medications (adrenaline, dopamine)
permits the administration of diluted irritating medications

Disadvantages

Overdose risk, Thrombophlebitis

- **Intramuscular (IM) Route**

Fig.no. (2) Intramuscular route



Injecting a drug into muscle tissue, which has a healthy blood supply, allows for quicker absorption[5].

Sites

Deltoid: less than two milliliters < 5 mL in the thigh

Gluteal: less than 5 mL

Advantages

Ideal for depot preparations (long-acting antipsychotics, for example)

Drug absorption is consistent and reliable.

Less irritation compared to the SC route

Disadvantages

Injection site pain, Damage to the sciatic nerve.

The development of an abscess is conceivable[5].

- **Subcutaneous (SC) Route**

Fig. no. (3) Subcutaneous route

Drug injected into the subcutaneous fatty tissue beneath the skin.

Advantages

Slow and sustained absorption

Suitable for self-administration (insulin, heparin)

Disadvantages

Only non-irritant, small-volume drugs, Necrosis with irritating drugs.

Absorption decreases in shock.

- **Intradermal (ID) Route**

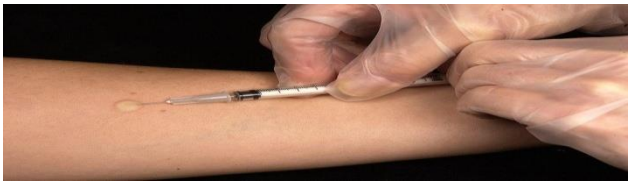


Fig.no. (4) Intradermal route

Medication injected (very superficially) into the dermis.

Sites

The inner forearm, The upper back

The volume 0.1 millilitres,0.2 milliliters

Uses

Test for tuberculin (Mantoux/PPD)

Testing for allergies, certain vaccinations.

❖ **Specialized Parenteral Routes**

- **Intra-arterial (IA):** Medications injected straight into an artery to target a specific organ or tissue (high local effect, lower systemic exposure).

Uses: Tumor-specific chemotherapy**,** Angiography diagnostic agents.

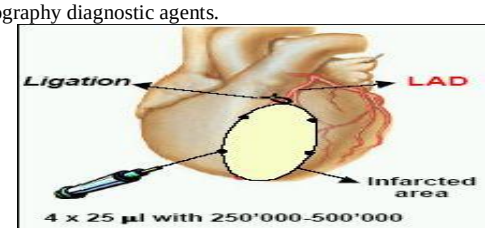


Fig. no. (5) Intra-arterial route

- **Intrathecal (IT):** Injection into the subarachnoid space's cerebrospinal fluid (CSF).

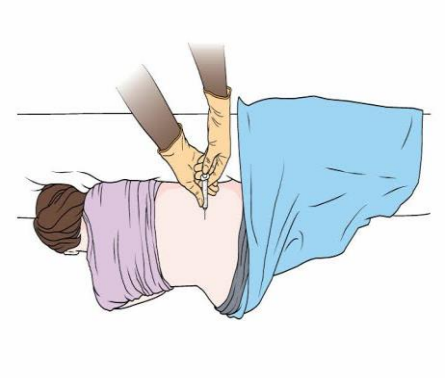


Fig. no. (6) Intrathecal route

Uses
Anesthesia of the spine.
Methotrexate chemotherapy.
Meningitis and antibiotics (rare).

- **Intraosseous (IO):** When an IV fails, it is injected into a bone marrow emergency access.
- **Intraperitoneal (IP):** Intraperitoneal (IP) means administration into the peritoneal cavity (the space inside the abdomen that houses organs like the intestines, liver, etc.)[7].

❖ **Pulmonary Route of Drug Administration**

Introduction
The pulmonary route is inhaling medication straight into the lungs. The lungs are an efficient route for both local and systemic drug delivery because of their enormous surface area (~70–140 m2), thin alveolar membrane, and copious blood supply.

Anatomy Relevant to Drug Delivery
Nasopharynx and larynx in the upper respiratory tract
Nasopharynx and larynx in the upper respiratory tract
The primary location of systemic absorption is the alveoli.
Rapid absorption is made possible by the alveolar epithelium's thickness of 0.1–0.2 µm[7,8].

Mechanisms of Drug Deposition in the Lungs
The walls of the upper airways are impacted by large particles (> 5 µm).
Bronchi and bronchioles are where medium particles (1–5 µm) settle.

Diffusion
Deep alveoli are reached by tiny particles (less than 1 µm)[9,10].
1–5 µm is the ideal particle size.

Dry Powder Inhalers (DPIs)
Breath-driven, medication in powder form that has been finely micronized.
Propellant is not required[11,12].

❖ **Nasal Route of Drug Administration**

Drug delivery via the nasal cavity for local, systemic, or nose-to-brain effects is known as the nasal route. Drugs entering through this route can be quickly absorbed without first-pass metabolism due to the nasal mucosa's high vascularity[12,13].

Mechanisms of Absorption
1. Lipophilic medications via the transcellular route
2. Hydrophilic medications via tight connections via the paracellular route
3. Transport via carriers: peptides and amino acids
4.Transcytosis and endocytosis: macromolecules
5. Direct transfer from the nose to the brain through the olfactory nerve via the trigeminal nerve[14,15].

Advantages of Nasal Route
Self-administration, non-invasive
Appropriate for emergency medications, Naloxone, Midazolam, Glucagon
Permits transport from the nose to the brain[16,17].

Limitations
Limited volume (0.1–0.2 mL per nostril)
High mucociliary clearance → short residence time
Absorption varies with colds, rhinitis, allergic conditions]18,19].

❖ **Ocular Route of Drug Administration**

Delivering medications directly to the eye for both local therapeutic impact (most common) and sporadic systemic absorption (minimum) is known as the ocular route. Glaucoma, infections, allergies, inflammation, and dryness can all be treated with ocular administration[20].

Mechanisms of Ocular Drug Absorption
A balance between hydrophilicity and lipophilia facilitates penetration.
B. Non-Corneal Pathway: Conjunctiva → Sclera → Ciliary body, Better for big and hydrophilic compounds.

Advantages of Ocular Route
1. Drug delivery directly to the place of action
2. Increased ocular focus with low systemic exposure
3. Topical versions (like mydriatics) have a quick onset.
4. Prevents metabolism in the first pass
5. Permits the use of implants with sustained release, such as Ozurdex[18]

Limitations
1. Extremely poor bioavailability, usually less than 5%
2. The medication is swiftly removed by blinking and diluting tears.
3. Hydrophilic and big medicines are restricted by the corneal barrier
4. Systemic absorption through nasolacrimal drainage
5. Standard eye drops have a short half-life
5. The half-life of conventional eye drops is brief.

❖ **Vaginal Route of Drug Administration**

Drugs are administered via the vagina for either systemic or local therapeutic effects. It is a successful alternative route for women because of its large surface area, rich blood supply, and avoidance of first-pass metabolism.

Anatomy Relevant to Vaginal Drug Delivery
Stratified squamous epithelium lines the fibromuscular tube that is the vagina.
Area of surface: ~60–80 cm²
Age of reproduction: 4.0–5.0 (acidic because of lactobacilli) 6–7 years after menopause.

Volume of vaginal fluid: 2-3 mL
Structure of the Vaginal Mucosa
1. The epithelium
2. The lamina propria
3. The layer of muscles

Mechanism of Drug Absorption

Medication is mostly absorbed through the

1. Transcellular Route

Drugs that are lipophilic spread throughout epithelial cells.

2. Paracellular Route

Tight junctions are traversed by hydrophilic molecules.

3. Lymphatic Absorption

Aids in avoiding first-pass metabolism.

4. Local Action

Mucosal contact for the treatment of hormonal problems, dryness, and infections.

Advantages of Vaginal Route

1. Prevents metabolism in the first pass
2. Fit for both systemic and local delivery
3. Low enzymatic activity is beneficial for proteins and peptides.
4. Capable of delivering hormones, contraceptives, and antimicrobials
5. Prolonged use of mucoadhesive gels
6. Painless and self-administration
7. Drug stability is enhanced by pH buffering formulations [20]

Limitations

1. Changes in the pH of the vagina
2. Drug absorption is impacted by variations in the menstrual period
3. Messiness and leakage from creams and liquids
4. Restricted capacity (2–3 mL)
5. Cultural restrictions or discomfort may affect certain women.
6. Some peptides can still be broken down by enzymes.
7. Certain medications cannot be used during pregnancy or certain infections[20].

❖ **Emerging Delivery Platforms (e.g., microneedles, nanoparticles)**

Emerging drug delivery platforms are cutting-edge technologies intended to increase patient compliance, boost therapeutic efficacy, and get around the drawbacks of traditional dose forms such low bioavailability, quick clearance, toxicity, and poor solubility. Microneedles, nanoparticles, liposomes, dendrimers, exosomes, long-acting injectables, and stimuli-responsive ("smart") systems are some of these cutting-edge technologies that offer special benefits for focused, regulated, and effective drug administration.

I. Microneedle-Based Delivery Systems

Microneedles (MNs) are micron-sized projections (50–900 μm) that enable for painless, minimally invasive medication delivery by puncturing the stratum corneum without reaching deeper nerve terminals.

Types

Solid MNs: Improve medication penetration by pretreating the skin.
Coated MNs – Drug coated onto the needle dissolves in skin.
Dissolvable MNs: Drug is released when biodegradable polymers disintegrate.
Hollow MNs: Provide liquid formulations in the form of small injections.
Hydrogel-forming MNs: They expand and progressively release medication.

Applications

Vaccines: COVID-19, hepatitis B, and influenza
Delivery of insulin for diabetes
Localised administration of cancer therapies
Delivery of DNA/RNA for gene therapy.

II. Nanoparticle Drug Delivery Systems

Drug encapsulation, improved solubility, target-specific delivery, and less systemic toxicity are all possible with nanoparticles (1–1000 nm)

Types

Polymeric nanoparticles (chitosan, PLGA)
mRNA COVID-19 vaccines employ lipid nanoparticles (LNPs)
Nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN)
Gold, silver, and iron oxide nanoparticles
Nanoparticles with dendritic structures
Emulsions in nanoscale
Systems based on graphene and carbon nanotubes.

Applications

Cancer treatment (paclitaxel nanoparticles, doxorubicin)
Gene therapy (mRNA, DNA, and siRNA)
Functionalised nanoparticles for CNS delivery
Delivery of antimicrobials
Delivery of vaccinations (mRNA vaccines based on LNP)

Conclusion

Drug delivery systems play a decisive role in determining the therapeutic success, safety, and patient acceptability of pharmaceutical agents. The choice of an appropriate route and delivery strategy directly influences bioavailability, onset of action, drug stability, and targeting efficiency. Conventional routes such as oral and parenteral administration remain the backbone of therapy due to their reliability and established clinical use; however, each presents inherent limitations, including first-pass metabolism, enzymatic degradation, invasiveness, and patient discomfort. Alternative routes such as pulmonary, nasal, ocular, vaginal, intrathecal, intra-arterial, and intraperitoneal administration have expanded therapeutic possibilities by enabling localized delivery, rapid absorption, and avoidance of gastrointestinal degradation.

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