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Review Article: Pathways to Precision: Advancing the Understanding of Drug Administration Methods

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Abstract: *This review explores various routes of drug administration, discussing their advantages, limitations, and applications. It emphasizes the importance of choosing the appropriate route based on pharmacokinetics, patient condition, and the nature of the drug, aiming to provide an in-depth understanding of the current landscape in drug delivery. The route of drug administration plays a pivotal role in determining the efficacy, onset, and overall therapeutic outcome of medications. This review comprehensively explores the diverse pathways through which drugs are introduced into the human body, highlighting their mechanisms, advantages, limitations, and applications. Broadly categorized into enteral, parenteral, and topical routes, each method is tailored to specific clinical needs based on factors such as the physicochemical properties of the drug, patient condition, and desired therapeutic goals. Innovations in drug delivery, including transdermal systems, inhalation devices, and targeted delivery techniques, have further expanded the scope of administration, enhancing precision and minimizing adverse effects. The review also emphasizes the importance of patient compliance, bioavailability considerations, and the impact of administration routes on pharmacokinetics and pharmacodynamics. By delving into traditional methods such as oral and intravenous routes alongside emerging technologies like nanocarriers and implantable devices, this paper aims to provide a holistic understanding of drug administration. The insights presented herein offer valuable perspectives for clinicians, researchers, and pharmaceutical developers, fostering advancements in drug delivery systems to optimize therapeutic outcomes and improve patient care.*

Keywords: Intranasal administration, Drug delivery, intravitreal injection, ocular drug delivery, nanoparticle, implant, hydrogel , ICA, Sex difference, Intra-arterial injection, Rodent

I. INTRODUCTION

A medication administration route is often classified by the location at which the drug is administered, such as oral or intravenous. The choice of routes in which the medication is given depends not only on convenience and compliance but also on the drug's pharmacokinetics and pharmacodynamic profile. Therefore it is crucial to understand the characteristics of the various routes and associated techniques. Many interprofessional healthcare team members are involved in administering medications to patients.[1]

There are many different drug routes of administration. Some are commonly used, while others are rare. Drug administration can be:

oral, which is when a person swallows a drug
intraocular, or into the eye
intraotic, or into the ear
nasal, or through the nose
sublingual, or under the tongue
buccal, between the gums and the mouth cheek
inhaled through the respiratory system
enteral, which is when a person receives the drug directly into their digestive tract
rectal, or through the rectum

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vaginal, or through the vagina
transdermal, or through the skin
subcutaneous, or under the skin
intramuscular, or via an injection into a muscle
intravenous, or into a vein
intra-arterial, or into an artery
intraosseous, or into the bone marrow
Intraperitoneal
Intrapulmonary

The Biopharmaceutical Classification System.

The Biopharmaceutics classification system (BCS) has been one of the most significant prognostic tools created to promote product development in recent years.[4] It is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability characteristics, which will substantially facilitate drug product selection and approval process for a large group of drug candidates. The goal of the BCS is to function as a tool for developing in vitro dissolution specifications for drug products that are predictive of their in vivo performance.[5] According to the BCS, drug substances are classified as follows: Class 1: High Solubility-High Permeability: generally very well-absorbed compounds Class 2: Low Solubility-High Permeability: exhibit dissolution rate-limited absorption Class 3: High Solubility-Low Permeability: exhibit permeability rate-limited absorption Class 4: Low Solubility-Low Permeability: very poor oral bioavailability.

This article gives an overview of the nose-to-brain route, focusing on the anatomy of nasal cavity and the cellular and molecular mechanisms playing an important role in the nasal drug administration and drug penetration to the brain. After this introductory part various in vitro, ex vivo and in vivo models for investigation of intranasal drug delivery will be presented based on the latest literature of the field. Then some studies which evaluate the intranasal penetration of drugs for different CNS indications will be shown. Finally the methods to improve the nasal drug delivery will be summarized and a critical evaluation of the nasal drug administration route will be given based on the limitations and the advantages of this technique.

Oral Drug Administrations

Oral drug administration involves a person putting a drug into their mouth and swallowing it. It is one of the most commonTrusted Source routes of drug administration, and it is convenient for many as it does not require special equipment. People can use oral administration for a range of medication types, such as pills, capsules, and liquids.

However, one of the downsides of oral administration is that it can be inefficient. The digestive system and liver start to break down drugs via this route before they reach the bloodstream, meaning the concentration significantly reducesTrusted Source. This is known as the “first pass effect.”

Additionally, some oral drugs can have adverse effects on the digestive system, and some people have difficulty swallowing pills.[2]

Oral administration is the most often used treatment for both systemic and local gastrointestinal diseases. Despite the apparent advantages, oral drug delivery remains challenging due to the harsh gastrointestinal tract (GIT) microenvironment and a number of physiological barriers, including gastrointestinal anatomy factors, biochemistry factors, and physiology factors. The different parts of the GIT, including mouth cavity, esophagus, stomach, small intestine, and colon, play an important role in the digestion of food and absorption of medicine. The different anatomical characteristics, such as limited surface in oral cavity, gastric mucin–bicarbonate barrier, and enteral enzymes could also be obstacles for drug absorption. Considerable efforts have been made to overcome these issues, which are mainly based on improved comprehension of the healthy and diseased physiology characters of the GIT. Conventional drug delivery systems including normal tablets, capsules, or sterile drug preparations, are associated with limitations, including low site-specific accumulation of drugs, unfavorable body distribution, adverse side effects, etc. Therefore, the development of novel localized and systematic targeted drug delivery systems is urgent. The application

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of nanomedicines and novel drug delivery devices were considered as the most promising innovative pharmaceutical approaches in oral drug delivery system

Most oral drug delivery systems also focused on targeting local gastrointestinal diseases, such as gastric diseases , oral carcinoma inflammatory bowel disease (IBD) and colon cancer , but with rapid development of pharmaceutical technology, materials science, and physiological study of diseases, tremendous advances have been made to develop oral targeted nanoparticle preparations that can target drugs to focal sites outside the GIT .. In this review, the biological factors that affect the oral administration and applications of nanomedicines and microfabricated devices in and beyond GIT are summarized.[3]

Oral Drug Delivery System: A Review hydration progress, the tablet continuous to swell until the wall breaks, forming a sandwich like structure. The release of drug processed primarily out of the side of the tablet as it passes through the intestinal tract. The tablet provides a nearly zero order drug release following a programmed period of delayed drug release. To achieved a constant zero order matrix sustained release formulation (COS Rx) for a poorly water soluble drug such as nifedipine (< 10ugml-1) a low mol.wt guargum was used. Channeling agents such as water-insoluble silicon dioxide water soluble lactose were used to enhance the porosity of the matrix aiding in the dissolution of drug. A combination of water soluble (Eudragit RLPO) and water insoluble polymer (Eudragit RSPO) in the ratio 1:9 (RL:RS) was used as coating material (2%w/w). the combination produced a lag time in drug release of 2 hrs.

Factor influencing performance of modified drugs formulation:

Food: The influence of food on the bioavailability of drug must be investigated for safety and efficacy. If any food effects are found then a justified dose with respect to the product intake in relation to meals is given4. Gastro- Intestinal function: By the modified release formulation is co- administrated with drug affecting GI tract physiology then investigation related to MR dosage form must be done. Diurnal Rhythms: Plasma concentration profile measured for 24 hrs at steady state of any difference occurs in view of Day/ night. Site of application: The absorption of drug at different site must be investigated of the application site in not limited to one body area. Dose dumping : The chances of unexpected release of drug resulting in unacceptable higher exposure occur when the MR formulation contains higher compared to immediate release product.[4]

Pathophysiological Factors Influencing Oral Drug Delivery

Adding to this complexity are the changes in gastrointestinal physiology associated with gastrointestinal or systemic disease, concurrent medications, and gastrointestinal surgery. These factors are dynamic, inter-related, and can further affect the efficacy of orally administered formulations. Therefore, they remain an important challenge in formulation design.

Physiological properties affecting drug absorption .

The successful functioning of oral medication depends primarily on how the gastrointestinal (GI) tract processes drugs and drug delivery systems. Many factors are involved in oral drug delivery, the measured oral bioavailability of a particular drug can be broken into components that reflect delivery to the intestine (gastric emptying, PH, food), absorption from the lumen (dissolution, lipophilicity, particle size, active uptake), intestinal metabolism (phase Ⅰ and/or phase Ⅱ enzymes), active extrusion (drug efflux pumps) and finally first-pass hepatic extraction. All these factors play an important role in the performance of orally administered dosage forms, and to understand how they affect oral drug absorption can greatly contribute to the drug discovery process. Principally, the rate of release of a drug from a dosage form within the GI tract should be considered. Drug dissolution, especially for poorly soluble drugs, is dependent upon the volume of juices available in the gastrointestinal tract, which are from the volume of coadministered fluids, secretions and water flux across the gut wall[6]. The volume of intestinal juices is important to estimate if a single dose can theoretically dissolve within the gut passage. [5]

Physicochemical factors affecting drug

solubility and permeability Solubility and intestinal permeability are the major physicochemical factors that affect the rate and extent of absorption of an oral drug product. Moreover, these two factors also closely interrelate with many

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other influential factors, such as lipophilicity, hydrophilicity, molecular size, polar van der Walls surface area, and so on, and thus act as the "final bridge" toward drug absorption. Therefore, making clear factors affecting solubility and permeability may be significantly important in drug product development and approval process for a large group of drug candidates

1. Solubility

The first requirement for absorption is dissolution of the active compound. Only compound in solution is available for permeation across the gastrointestinal membrane. Solubility has long been recognized as a limiting factor in the absorption process. By definition, solubility is the extent to which molecules from a solid are removed from its surface by a solvent. Aqueous solubility can be estimated by determining the ability of a drug to partition from lipid to aqueous environments, which is dependent on the ionization of drug tested. Most drugs are weakly acidic or weakly basic compounds that cannot ionize completely in aqueous media, while only partly ionize. Since drug ionization are greatly dependent on the solvent pH, the above partition behavior is often considered as a function of solvent pH, and pKa is often used as a parameter describing a compound's dissolution characteristic. In general, ionized drugs tend to exhibit far greater aqueous solubility than the un-ionized counterpart. As a result, the rate of solute dissolution in aqueous media can be markedly affected by the pH of the solvent.

antilog(pH-pKa) = [ionized][un-ionized] that is: % un-ionized = 1001 + antilog(pH-pKa) Weak base: antilog(pKa-pH) = [ionized][un-ionized] that is: % un-ionized = 1001 + antilog(pKa-pH)

2. Permeability

Permeability is another important factor in achieving desirable oral bioavailability. The above critical property of permeability should contribute to the correspondingly unique way about how substances (including drugs) "travel through" cellular membranes. So to discuss physicochemical properties affecting permeability, one need first get to know the structure of cellular membranes and how drugs pass through these membranes [5]

Advantages

Simple and convenient to use.
Drugs readily available by prescription.
Drug reactions are generally less severe.
Oral route less objectionable than parenteral.
Requires only minimal training.
Duration of action may extend into posttreatment period.

Disadvantages

Patient noncompliance.
Dosages are largely empirical.
Titration to clinical endpoint impossible.
Erratic absorption makes response unpredictable.
Level of sedation cannot be altered.
Not useful in extremely apprehensive patients.
Duration of action may extend into post treatment period [6]
Variable absorption rates
Degradation of some drugs before reaching the site of absorption into the bloodstream
The inability of many compounds to effectively traverse the intestinal epithelial membrane cells to reach the bloodstream.
The insolubility of many drugs at low pH levels is prevalent in the digestive tract.
The inactivation of the drug in the liver on its way to the systemic circulation
Irritation of the mucous lining of the gastrointestinal tract. This can be prevented to some extent by coating. [10]

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Intravenous and intramuscular administration

The intravenous (IV) administration route involves using a needle to inject a drug directly into a vein. The intramuscular route is similar but involves an injection into a muscle instead.

IV administration is suitable for many drugs, particularly in situations where a person needs an urgent, high, or consistent dose, such as during a severe infection. This is because IV drugs bypass the digestive system and take effect quickly.

Intramuscular administration also bypasses the digestive system, allowing the body to get a more potent dose of a drug. Some vaccines and hormone drugs have intramuscular administration options.

The downside of these methods is that they can cause pain, swelling, or irritation around the injection site. For people with needle phobias, they can be distressing. There is also a risk Trusted Source of complications, such as infection, nerve injury, hematoma, and accidental puncturing of a blood vessel.

Injections are among the most common health care procedures throughout the world, with at least 16 billion administered in developing and transitional countries each year.Citation1 Intravenous (IV) and intramuscular (IM) are two most frequently used injection routes in medication administration. IV injection is the introduction of a medication into the veins using a needle, and it is used when rapid absorption is called for, when fluid cannot be taken by mouth, or when the medication to be administered is too irritating to be injected into the skin or muscles. IM injection is the technique used to deliver a medication deep into the muscles, allowing the medication to be absorbed into the bloodstream quickly. Prescribing information for some medications notes that they can be injected via one or more routes (eg, epinephrine can be delivered by IV, IM, or SC route), while prescribing information for the majority of injectable medications only describes one injection route.

Epinephrine has a pivotal role as first-line treatment for acute anaphylaxis. Campbell et al compared rates of cardiovascular adverse events and epinephrine overdoses between various routes of epinephrine administration among patients with anaphylaxis in the emergency department. Occurrence rate of adverse cardiovascular events associated with IV bolus epinephrine was 10% compared with IM epinephrine (1.3%) (OR 8.7, P=0.006). Similarly, overdose occurred with IV bolus epinephrine compared with IM epinephrine (13.3% versus 0%; OR 61.3, P<0.001).Citation65 Therefore, there is a need for extreme caution and further education about IV bolus epinephrine in anaphylaxis[7]

Some medications must be given by an intravenous (IV) injection or infusion. This means they're sent directly into your vein using a needle or tube. In fact, the term "intravenous" means "into the vein."

With IV administration, a thin plastic tube called an IV catheter is inserted into your vein. The catheter allows your healthcare professional to give you multiple safe doses of medication without needing to poke you with a needle each time.

In most cases, you won't give yourself an intravenous medication. While you can take some infusion medications yourself at home, you'll likely receive your therapy from a healthcare professional.

Read on to learn about the two main tools used for IV administration — standard IV lines and central venous catheters — including why they're used and what the risks are.

IV push

An IV "push" or "bolus" is a rapid injection of medication. A syringe is inserted into your catheter to quickly send a one-time dose of a drug into your bloodstream.

IV infusion

An IV infusion is a controlled administration of medication into your bloodstream over time. The two main methods of IV infusion use either gravity or a pump to send medication into your catheter:

Pump infusion. In the United States, a pump infusion is the most common method used. The pump is attached to your IV line and sends medication and a solution, such as sterile saline, into your catheter in a slow, steady manner. Pumps may be used when the medication dosage must be precise and controlled.

Drip infusion. This method uses gravity to deliver a constant amount of medication over a set period of time. With a drip, the medication and solution drip from a bag through a tube and into your catheter.[8]

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Drugs typically given by IV

Many different types of medications can be given by IV. Some of the drugs more commonly given by this method include:

chemotherapy drugs such as doxorubicin, vincristine, cisplatin, and paclitaxel
antibiotics such as vancomycin, meropenem, and gentamicin
antifungal drugs such as micafungin and amphotericin
pain relief medications such as hydromorphone and morphine
drugs for low blood pressure such as dopamine, epinephrine, norepinephrine, and dobutamine
immunoglobulin medications (IVIG)

Side effects

While IV medication use is generally safe, it can cause both mild and dangerous side effects. Medications given intravenously act on your body very quickly, so side effects, allergic reactions, and other effects can happen fast.

In a 2020 study of 450 patients, 176 (39.11 percent) with peripheral IV placement had at least one problem. In most cases, a healthcare professional will observe you throughout your infusion and sometimes for a period afterward. Examples of IV side effects include

IV injections are one of the quickest and most controlled ways to deliver medications or other substances into the body. A healthcare professional may administer an IV injection in the following situations:

when a person needs a potentially life saving medication very quickly
when a person needs a very accurate dose of a medication
when a person needs a large dose of a medication over an extended period of time
when taking a medication by mouth would be impractical or ineffective
when a person would otherwise require multiple injections, such as when receiving treatments for some chronic conditions
when a person cannot eat or drink and requires fluids through an IV line

This directly administers the medications to the systemic circulation. It is indicated when a rapid drug effect is desired, a precise serum drug level is needed, or when drugs are unstable or poorly absorbed in the gastrointestinal tract. It is also the route utilized in patients with altered mental status or severe nausea or vomiting, unable to tolerate oral medications.

Advantages:

Rapid onset of action
Predictable way of action and almost complete bioavailability
The problems of oral drug administration can be eliminated by avoiding the gastrointestinal tract
The best way of administration in very ill and comatose patients who cannot ingest anything orally

Disadvantages:

Causes pain
Chance of infection
The delivery of protein products that require sustained levels can be difficult.

Intramuscular Route

This can be utilized when oral drug absorption occurs in an erratic or incomplete pattern, the drug has high first-pass metabolism, or the patient is not compliant.] A depot preparation of the drug can be given intramuscularly, and the medication dissolves slowly into the circulation to provide a sustained dose over a more extended time. An example includes haloperidol decanoate. Vaccines are also administered via the intramuscular route.

Intramuscular injection should be done at a perpendicular angle as it has been shown to be the most effective method for patient comfort, safety, and medication efficacy.[19] Skin traction and deep pressure on the muscle can help

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decrease patients' pain and discomfort] When injecting to the dorsogluteal site, aspirating for a few seconds is recommended, given its proximity to the gluteal artery.[10]

Intramuscular administration of substances is a common parenteral route in large animals and humans but often is avoided in smaller species because of the reduced muscle mass. Generally, intramuscular injections result in uniform and rapid absorption of substances, because of the rich vascular supply (Figure 3). Smaller volumes are administered intramuscularly than for subcutaneous delivery (Table 1). The intramuscular technique requires more skill than does subcutaneous injection and should be conducted only by well-trained personnel. Intramuscular injection of irritating substances or inadvertent injection of nerves may result in paresis, paralysis, muscle necrosis, and localized muscle sloughing.103 Repeated injections may result in muscle inflammation and necrosis.30 Other considerations and cautions for using the intramuscular route for substance delivery are similar to the subcutaneous route.[16]

Nasal drug administration

The nasal administration route involves spraying or sniffing a drug through the nose, where it quickly absorbs into the bloodstream.

This is a route of administration for drugs that work directly on nasal and sinus conditions, such as decongestant sprays. However, doctors can also prescribe it for other types of medical treatment. For example, some vaccines come in nasal forms.

The benefits of administering medications via the nose are that it is painless, delivers a high concentration of the drug, and allows drugs to take effect quickly.

However, only certain drugs work via nasal administration. Additionally, the dose and effect size may have limitations Trusted Source depending on the size and features of a person's nasal cavity and how they administer it. People may also make more mistakes with dosing nasal administration, affecting the dose they receive.

The nasal route is a promising alternative to the parenteral routes for drug administration. As a non-invasive route, nasal drug delivery offers numerous advantages, including avoidance of needle-stick hazards, circumvention of first-pass metabolism, ease of self-administration, and rapid absorption.1., 2., 3. It has also been argued that nasal drug delivery provides environmental advantages because it is likely to reduce the amount of non-biodegradable waste (e.g., disposable syringes) [13]

The nasal route is one of the most permeable and highly vascularized site for drug administration ensuring rapid absorption and onset of therapeutic action. It has been potentially explored as an alternative route for drugs with poor bioavailability and for the delivery of biosensitive and high molecular weight (MW) compounds such as proteins, peptides, steroids, vaccines, and so on. This review discusses the major factors affecting the permeability of drugs or biomolecules through the nasal mucosa, including biological, formulation and device-related factors. This information could potentially help to achieve desired plasma concentrations of drugs without compromising or altering the normal physiology of the nasal cavity.[12]

Many researchers have claimed the discovery of enhancers which will eliminate all nasal absorption problems. Similar claims have also been made for other routes of drug administration. In our opinion such claims may have some shortcomings. No single enhancer can be expected to solve absorption problems for all drugs. Why certain enhancers can improve absorption of certain drugs, is not well known. It is usually very difficult to precisely predict the right enhancer for a given drug formulation. [14]

Intranasal techniques may be used for either local (for example, vaccinations or decongestant sprays) or systemic delivery of substances. The nasal mucosa lines the nasal cavity and is richly supplied with blood vessels, potentially resulting in rapid substance absorption and subsequent systemic effects, avoiding the hepatic first-pass effect seen with oral delivery. Blood drug levels of substances administered intranasally may approach those seen after intravenous administration, and small, lipophilic molecules are absorbed more rapidly by this route than are large molecular weight or highly polar substances [16]

Characteristics of a nasal drug delivery optimizer

Many researchers have claimed the discovery of enhancers which will eliminate all nasal absorption problems. Similar claims have also been made for other routes of drug administration. In our opinion such claims may have some

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shortcomings. No single enhancer can be expected to solve absorption problems for all drugs. Why certain enhancers can improve absorption of certain drugs, is not well known. It is usually very difficult to precisely predict the right enhancer for a given drug formulation

Mechanisms of nasal drug absorption enhancement

As has been mentioned earlier in this paper, precise mechanisms of enhancer effects are not known. However, it is generally believed that enhancers may show their actions via one or both of the following mechanisms:

Classifications and examples of nasal drug delivery optimizers

In an attempt to optimize nasal drug absorption, researchers have explored several plausible chemical agents as potential nasal drug absorption optimizers. This has led to a large number of optimizers reported in the literature. It is difficult to precisely classify these agents in a meaningful manner because they often have overlapping chemical properties. In published reports on enhancers, different researchers have classified absorption optimizers differently [14]

Models for testing direct nose-to-brain delivery

Models of nasal drug delivery can be used for detecting and testing nasal drug absorption and permeation, for PK/PD studies, toxicological and electrophysiological studies, and also for assessment of drug transporter interaction and the nasal barrier

Models commonly used in nasal drug delivery experiments are in vitro, in vivo and ex vivo models. The different models can be used for various studies. in vitro techniques permit permeation and diffusion studies, while in vivo models are suitable for characterization of nasal absorption and also for pharmacokinetic profile determination of a drug and finally, ex vivo technique can be performed to study the nasal perfusion. All these models are given below.

1. In vivo models models
2. In vitro models
3. RPMI 2650 a cell culture model of the nasal barrier
4. CaCo-2 cell line
5. Ex vivo models [11]

Nanoparticles (nanosuspensions, nanoformulations)

A popular formulation method for many routes of administration is the formation of nanosuspensions of drugs encapsulated in polymeric carriers. These carriers may provide favorable characteristics to the drug like enhanced absorption, mucoadhesion and increased stability.

Drug name

Benzodiazepines (midazolam, diazepam), Insulin, Angiotensin II, Melanocortin proteins, Oxytocin, Orexin-A.

Advantages

Non-invasive
Low risks of infections
Easy self-administration
Relatively large absorption area (160 cm2 in humans; 13.4 cm2 in rats)
Large olfactory epithelium area (especially in rodents) (12.5 cm2 in humans; 6.75 cm2 in rats)
Rapid absorption
Nasal submucosa is abundant in vascular and limphatic vessels
No hepatic first pass metabolism of the drugs
Direct drug delivery to the brain bypassing the blood-brain barrier

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Limitations

Active mucociliary clearance
Short retention time
Enzymatic degradation by nasal cytochrome P450/peptidases/proteases (pseudo first pass effect)
Low permeability for hydrophilic drugs
Absorption enhancers needed
Low nasal epithelial pH
Interindividual variability
Low CNS delivery for proteins
Nasal secretion has an influence on the absorption [11]

Sublingual and buccal administration

The sublingual administration route is when a person places the drug under the tongue, where it absorbs into the bloodstream. The buccal administration route works in a similar way, but a person places the drug between the gum and the inside of their cheek instead.

Both of these routes are typically simple and painless. The drugs absorb quicklyTrusted Source, meaning a medication can start working quickly. They can be good alternatives to oral administration for people who have difficulty swallowing or with digestion.

Sublingual and buccal administration can be difficult if the drug tastes unpleasant. There are also relatively few drugs that are available with this route of administration, and if a person does not allow the drug to dissolve fully, it will affect their dose.

Some people take certain vitamins sublingually. This method can also be useful for delivering immunotherapy for allergies. Buccal administration is the method of delivery for some nicotine replacement products and strong pain medications, such as fentanyl.

These are indicated for medications with high first-pass metabolism that need to avoid clearance by the liver. For instance, nitroglycerin is cleared more than 90% during a single pass through the liver; therefore, it is given in a sublingual form.

Advantages

Rapid absorption is due to the abundant mucosal network of systemic veins and lymphatics, thereby leading to a rapid onset of action.
If there is any untoward event, the tablet can be removed.
Avoids first-pass hepatic metabolism.
A tablet can be kept for a long time in the buccal cavity, which helps develop formulations with a sustained-release effect.
This route is useful in patients having swallowing difficulties.
Low risk of infection
Convenience

Disadvantages

The tablet must be kept in the buccal cavity and neither chewed nor swallowed.
Excessive salivation may cause quick dissolution and absorption of the tablet.
Patients may find it difficult to accept an unpalatable tablet. Hence some drugs are applied as a patch or a spray. [10]

Transdermal and subcutaneous

Transdermal administration is when a drug enters the body through the skin, such as via a cream, gel, ointment, or patch. Subcutaneous administration is when a person uses a needle to inject the drug underneath the outer layers of the skin.

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Transdermal administration is simple, noninvasive, and painless. Uses include nicotine replacement therapy, hormonal medications, and hormonal contraceptives.

However, the downside of this route is that transdermal application can irritate the skin, and not all drugsTrusted Source absorb effectively this way. Additionally, the condition of the skin may affect absorption. For example, if it is dry or has open cuts, it may absorb too much or too little.

Subcutaneous administration is typical for insulin and the anaphylaxis medication known as epinephrine. Because this level of the skin has few blood vesselsTrusted Source, this option allows for a slow release of drugs. However, it is invasive and can be painful.

Transdermal delivery is gaining interest as an option for drug administration. The drug reaches the systemic circulation through the skin without losing the drug during reaching its target, enhance the bioavailability, improving sustained drug release, minimizing undesirable side effects, and improving physiological and pharmacological response . For instance, in testosterone replacement studies, transdermal delivery overcomes the issues associated with oral and intramuscular delivery, it bypasses the hepatic first-pass after oral administration, and thus reduce the required dose. Besides, it eliminates the need for recurring injections and a higher concentration of testosterone in the blood , Tajbakhsh et al., Nevertheless, the delivery of drugs via the transdermal administration route is highly affected by the chemical properties of drugs, which affects absorption through the SC. Hence, few drugs can be delivered in significantly therapeutic amounts via this route . [17]

Subcutaneous Route

This is used when the drug's molecular size is too large to be effectively absorbed in the intestinal tract or when better bioavailability or a faster absorption rate is needed than the oral route. It is easy to administer and requires minimal skills, so patients can often self-administer the medication. Common medications administered subcutaneously include insulin, heparin, and monoclonal antibodies. The rate of absorption of drugs through this route can be enhanced by infiltration with the enzyme hyaluronidase.

The major factors that affect the rate of absorption by this route include the size of the molecules (large molecules having slow penetration), viscosity, and the anatomical characteristics of the site of injection (vascularity and amount of fatty tissue).

Disadvantages

The rate of absorption is difficult to control.

Local complications - irritation and pain.

Injection sites must be changed frequently to prevent the buildup of unabsorbed medication, which could lead to tissue injury[10]

Vaginal drug administration

The vaginal administration route involves inserting a drug into the vagina, where it gradually absorbs into the bloodstream. The drug may come in the form of a suppository, cream, gel, or capsule.

Vaginal administration can be useful for medications that act locally, such as antibiotic or antifungal medications for infections or hormone treatments for vaginal dryness or atrophy. It is also a route for some systemic drugs that affect the whole body.

Vaginally-absorbed drugs can be easy to administer and are typically painless, but the drug may cause discomfort if it is a solid suppository. A 2019 study also notes that factors such as vaginal pH and flora could influence the effectiveness of drugs.

This is not commonly used but can deliver low, continuous dosing of medications which can help achieve stable drug levels. A variety of formulations can be given vaginally, including tablets, creams, gels, ointments, and pessaries. Common medications given via the vaginal route include vaginal estrogen therapy for urogenital atrophy, contraceptive rings, antibiotics, or antifungals.

Position the patient onto their back with legs bent and feet resting flat on the bed. A lubricant can be used to reduce friction against the vaginal mucosa as the medication is administered. Gently separate labial folds with the non-

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dominant gloved hand while with the dominant gloved index finger, insert the lubricated suppository to about 8-10 cm along the posterior vaginal wall. [10]

Scientists around the globe have done cutting-edge research to facilitate the delivery of poorly absorbed drugs via various routes of administration and different delivery systems. The vaginal route of administration has emerged as a promising mode of drug delivery, attributed to its anatomy and physiology. Novel drug delivery systems overcome the demerits of conventional systems via nanobiotechnology. This review will focus on the disorders associated with women that are currently targeted by vaginal drug delivery systems. In addition, it will provide insights into innovations in drug formulations for the general benefit of women.[25]

Exhaustive efforts have been made toward the administration of drugs, via alternative routes, that are poorly absorbed after the oral administration. The vagina as a route of drug delivery has been known since ancient times. In recent years, the vaginal route has been rediscovered as a potential route for systemic delivery of peptides and other therapeutically important macromolecules. However, successful delivery of drugs through the vagina remains a challenge, primarily due to the poor absorption across the vaginal epithelium. The rate and extent of drug absorption after intravaginal administration may vary depending on formulation factors, vaginal physiology, age of the patient and menstrual cycle. Suppositories, creams, gels, tablets and vaginal rings are commonly used vaginal drug delivery systems. The purpose of this communication is to provide the reader with a summary of advances made in the field of vaginal drug delivery. This report, therefore, summarizes various vaginal drug delivery systems with an introduction to vaginal physiology and factors affecting drug absorption from the vaginal route.[26]

Advantages of vaginal drug administration

Like some other non-oral drug-delivery methods, vaginal systems (e.g., suppositories, gels, vaginal rings) aim to provide not only a localized effect, but through drug absorption, sustained therapeutic levels compared with the traditional oral route. Vaginal administration enables the use of prolonged dosing regimens, lower daily doses, and continuous release of medication.Longer intervals between doses are generally welcomed by patients as a more convenient alternative to daily intake, and this can enhance regimen compliance. There is evidence that a substantial proportion of oral contraceptive users become tired of taking pills on a daily basis, particularly over a number of years. It has also been shown that the number of missed pills increases over time as women “learn” that they can miss pills and then do. Efforts to develop alternative hormonal delivery systems are ongoing and include injectables, implants, and intrauterine devices (IUDs), with the recent introduction of the weekly transdermal patch and the monthly vaginal ring for contraception. The advantage of the transdermal patch and the vaginal ring over implants, IUDs, and injectables is that women are in control of their method, making use of the products more easily reversible. Although the pill is also user controlled and can be used in the vagina, the vaginal ring has the advantages of being nondaily, with constant serum levels.the major advantages of vaginal administration over oral administration is that drugs avoid gastrointestinal (GI) absorption and the hepatic first-pass effect. Absorption from the GI tract can be unpredictable and may be compromised by vomiting, drug–drug interference, or decreased intestinal absorption capacity. Moreover, the GI lumen and the liver are sites of elimination for many compounds. Avoidance of the hepatic first-pass effect is particularly advantageous for compounds that undergo a high degree of hepatic metabolism. For example, natural estrogens are 95% metabolized by the liver when administered orally. The potential benefits of vaginal drug delivery over oral, therefore, include lower dosing and lower systemic exposure plus lower incidences of side effects while achieving the same pharmacodynamic effect. [27]

Enteral drug administration

Enteral drug administration refers to any method that delivers a medication to the intestines. This includes oral administration, but also other approaches, such as:

through the nose and into the stomach via a nasogastric (NG) tube

through the nose into the intestines via a nasointestinal (NI) tube

through the skin into the stomach via a percutaneous endoscopic gastrostomy (PEG) tube

Another method of enteral administration is inserting a drug into the rectum, such as via a suppository or enema.

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Each of these methods has its own uses and risks. NG, NI, and PEG tubes can be essential for drug administration in situations where a person cannot eat, as it allows doctors to deliver oral medications directly into the stomach or intestines.

Some examples of drugs that can require rectal administration include certain laxatives, and diazepam during a seizure. This route can deliver drugs quicklyTrusted Source but can also be uncomfortable, and some drugs may irritate the rectum.

Administration of substances directly into the mouth, admixed in diet or other foodstuffs, or by orogastric or nasogastric gavage is common in laboratory animal medicine and research. Per rectum administration of substances by enema or suppository is less common in animals than in humans. The oral route is economical, convenient, relatively safe, and some animals can be trained to cooperate voluntarily, depending on the compound being administered. Although voluntary consumption of the material being administered is ideal, this dosing technique may not be reliable in all animals or dose groups or for long-term studies, because of individual preferences for flavors, palatability issues, and changes in behavior over time. For substances being tested for safety, oral dosing mimics the most commonly used mode of administration of substances to humans. When placing substances directly into the mouth, it is important to ensure that tablets or gelatin capsules containing test material are placed far back in the mouth and that the animal swallows, to ensure receipt of the full dose. The number and size of capsules or tablets administered should be proportional to the size of the animal being dosed, to minimize regurgitation. Gavage (esophageal or gastric) is often used in research settings, instead of mixing substances in water or food, to ensure precise and accurate dosing of animals [16]

Intraocular drug administration

Retinal diseases, such as neovascular age-related macular degeneration (AMD), diabetic retinopathy, and retinal vascular disorders, are the leading causes of vision deterioration in most developed countries. The recent development of anti-vascular endothelial growth factor (anti-VEGF) treatments has markedly suppressed disease progression. Current anti-VEGF drugs, including bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA), ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA, USA), and aflibercept (Eylea; Regeneron, Inc., Tarrytown, NY; and Bayer Healthcare Pharmaceuticals, Berlin, Germany) are manufactured as humanized monoclonal antibodies. However, according to their intraocular pharmacokinetic properties, these biologic drugs have relatively short half-lives, thereby requiring monthly or bi-monthly injections to maintain their efficacy in the intraocular space. Although anti-VEGF treatment is effective and beneficial for numerous retinal disorders, frequent intravitreal drug injections become a significant treatment burden to patients and the healthcare system owing to the overall cost and invasive technique utilized

Efforts to Enhance the Intraocular Pharmacokinetics and Pharmacodynamics of Intravitreal Drugs

This section presents previous, current, and future investigations that aim to enhance the intraocular pharmacokinetics and pharmacodynamics of intravitreal drugs. From dose escalation to intravitreal implants and tissue engineered nanoparticles, cutting-edge techniques and advancements have been accomplished.[15]

Intraocular Pharmacokinetics of Current Intravitreal Drugs

The intravitreal drugs that are currently administered globally for retinal diseases are ranibizumab, bevacizumab, aflibercept, brolucizumab, faricimab, and conbercept. These VEGF inhibitors are produced as recombinant humanized monoclonal antibodies, such as ranibizumab (antigen-binding fragments, Fab, molecular weight 49 kDa) and bevacizumab (IgG, molecular weight 148 kDa), and fusion proteins such as aflibercept (Fc, molecular weight 145 kDa). Previous studies have investigated the intraocular pharmacokinetics of anti-VEGF drugs to achieve maximal treatment efficacy

In addition to pre-clinical animal studies, pharmacokinetic parameters in human eyes have also been measured. Krohne et al. calculated the intraocular pharmacokinetics after a single intravitreal injection of bevacizumab and ranibizumab [26,27]. The aqueous half-life of bevacizumab was 9.82 days while that of ranibizumab was 7.19 days in human non-

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vitrectomized eyes. Both drug concentrations peaked on the first day after injection to the aqueous humor and declined monoexponentially [15]

Epidural and intrathecal administration

For rapid effects of substances on cerebrospinal tissues or meninges, substances can be administered into the epidural or subarachnoid (intrathecal) space of the spinal cord .This technique avoids absorptive problems otherwise presented by the blood–brain barrier. The route is used commonly to induce spinal anesthesia or to introduce contrast media for visualizing vertebral bodies or the spinal cord of large animal species. The technique requires animals to be sedated heavily and given a local anesthetic block over the spinal needle insertion site; alternatively animals can undergo general anesthesia prior to implementation.23,138 Aseptic preparation of the skin overlying the injection site and use of sterile technique for needle insertion are critical for success and animal recovery. The exact location of needle insertion and volume of injectate will vary between species and for intrathecal compared with epidural administration, and several factors contribute to procedural success. Epidural fat, lipophilicity of the substance being administered, leakage of injectate through intervertebral spaces, and pronounced meningovertebral ligaments all will limit or alter the spread of material being introduced by epidural or intrathecal routes. This limitation may be problematic, in that increased quantities of substances may need to be administered for effect, with the possibility of spill-over into systemic circulation, resulting in adverse effects, such as profound respiratory depression requiring prolonged ventilation. Visualization of cerebrospinal fluid after spinal needle insertion confirms intrathecal placement of the needle. If this fluid is noted when attempting an epidural injection, the needle should be withdrawn and repositioned, or the dose of the substance administered should be reduced, because the kinetics of substance absorption from epidural compared with intrathecal delivery can be markedly different.[16]

Intraperitoneal administration.

Injection of substances into the peritoneal cavity is a common technique in laboratory rodents but rarely is used in larger mammals and humans. Intraperitoneal injection is used for small species for which intravenous access is challenging and it can be used to administer large volumes of fluid safely or as a repository site for surgical implantation of a preloaded osmotic minipump. Absorption of material delivered intraperitoneally is typically much slower than for intravenous injection. Although intraperitoneal delivery is considered a parenteral route of administration, the pharmacokinetics of substances administered intraperitoneally are more similar to those seen after oral administration, because the primary route of absorption is into the mesenteric vessels, which drain into the portal vein and pass through the liver. Therefore substances administered intraperitoneally may undergo hepatic metabolism before reaching the systemic circulation. In addition, a small amount of intraperitoneal injectate may pass directly across the diaphragm through small lacunae and into the thoracic lymph.

In mammals, intraperitoneal administration typically is conducted in conscious animals by using firm manual restraint, with the head and body tipped downward to move viscera away from the surface of the ventral abdomen. Injections in rodents are made in the lower right abdominal quadrant away from the midline to avoid inadvertent injection into the urinary bladder or cecum. The syringe plunger may be withdrawn prior to injection, specifically looking for urine, blood, or digesta in the needle hub; if these fluids are seen, the needle should be withdrawn, replaced, and repositioned prior to injection. The most common mistake is to puncture the skin at too acute an angle, resulting in subcutaneous rather than intraperitoneal administration. For intraperitoneal injections in fish, the animals are restrained on their side on a flat surface, and the needle should enter along the midline, just anterior to the pelvic fins. Larger fish may require sedation or light anesthesia for appropriate restraint.

Materials injected intraperitoneally should be sterile, isotonic, and nonirritating. Irritating substances injected intraperitoneally may induce painful ileus and peritonitis in rodents, with subsequent adhesions.This drawback is typified by the effects of undiluted chloral hydrate when administered intraperitoneally in rats. Injections of identical doses of chloral hydrate in less concentrated solutions may avoid peritoneal irritation, and this technique may be used for other potentially irritating substances. Although technically a simple procedure to perform, training and competency of personnel should be monitored to ensure that substances are delivered accurately and that inadvertent intracecal or intracystic injections are avoided. [16]

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Intrapulmonary drug administration

Intrapulmonary drug administration: Involves delivering drugs directly into the lungs. This route is typically used for conditions affecting the lungs (e.g., asthma) or for rapid systemic absorption through the lung's large surface area.

Intrapulmonary delivery to other species is accomplished by either intratracheal instillation or inhalation. Intratracheal instillation is an easier delivery method requiring less specialized equipment and knowledge; however, this route typically is not as effective as are inhalational techniques in ensuring even pulmonary exposure to a substance. Intratracheal instillation involves injecting small volumes of solutions directly into the trachea of anesthetized animals and results in rapid but localized and uneven distribution of material over a relatively small volume of the lung. Volumes administered by the intratracheal route must be small to avoid suffocation. Those performing the intratracheal technique should be competent at intubating the species being treated, or a surgical cutdown can be used to expose the trachea for direct injection. [16]

Intraperitoneal delivery represents a theoretically easy method of introducing material into rodents, but the associated accuracy can be questionable. In one study in rats, 19.6% of intraperitoneal injections conducted by competent staff resulted in the material being injected in the gastrointestinal tract, subcutaneously, retroperitoneally, or into the urinary bladder. In addition, the true prevalence of associated complications likely is underestimated, given that many animals are not necropsied after injection. Potential complications include infection, pain, local irritation and chemical peritonitis, formation of fibrous tissue and adhesions within the abdominal cavity, perforation of an abdominal organ, hemorrhage, and respiratory distress or discomfort from administration of too large a volume. Repeated administration can result in a cumulative irritant effect and needle-induced damage [16]

Intraperitoneal administration of test compounds is attractive in view of the simplicity of the procedure. However, the injection method must be carefully controlled. Absorption occurs rather rapidly but compounds are (partially) subjected to hepatic first-pass elimination. The effect of biopharmaceutical and biological factors on drug bioavailability is known only to a limited extent. Non-specific side effects may occur in response to both the vehicle and the test compound. Certainly repeated [18]

There is increasing scientific evidence to substantiate using low-dose glucagon as a supplement to insulin therapy in artificial pancreata for diabetes mellitus type 1. The delivery of both these hormones intraperitoneally would mimic normal physiology.[19]

Background Intraperitoneal drug administration applies treatment at the site of diseases with gynaecological, urological, or gastrointestinal origin. The objective of this systematic review was to investigate perioperative intraperitoneal administration of antibacterial agents to characterise the drugs used and their safety profile [20]

Different techniques involving the administration of intraperitoneal chemotherapy have been reported including early postoperative, closed intraoperative, the open or coliseum technique, and the open technique using a PCE device. All techniques have been associated with low mortality and morbidity that is significant, but generally consistent with other major surgical procedures. [21]

The current technology for administering intraperitoneal heated chemotherapy is expensive and, for some institutions, unaffordable. We conducted this study to assess the temperature stability provided by a modified, inexpensive system, to offer a simple and low cost alternative to the standard HIPEC delivery equipment.[22]Pharmacokinetic studies have shown an important dose advantage for intraperitoneal versus intravenous application. Hyperthermia enhances the penetration of cytostatic drugs into tumour tissue and also shows synergism with various cytostatic drugs. The penetration depth of drugs into tissue is limited, therefore HIPEC can only be effective in patients with minimal residual disease after (aggressive) surgery. HIPEC can be conducted in various ways, without clear proven advantage of one method over the others. Local complications after this combined treatment approach are mainly surgery related. Intraperitoneal chemotherapy may cause systemic toxicity, dependent on the drug used. In randomised studies cytoreductive surgery followed by HIPEC has proven its value in the prevention of peritoneal dissemination in gastric cancer. Phase II data on HIPEC in peritoneal carcinomatosis of colorectal origin and pseudomyxoma peritonei are promising, but randomised studies are still not available.[23]

CPT-11 is clearly one of the most important new anticancer drugs developed in the last few decades, and CPT-11 combined with 5-fluorouracil (5-FU) and leucovorin is considered as reference first-line chemotherapy in the treatment of metastatic colorectal cancer. CPT-11 has a complex pharmacologic profile in vivo, and it needs caboxylesterase-

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mediated biotransformation to SN-38 before production of its cytotoxic effect. Intraperitoneal administration of CPT-11 has been studied recently in murine models and presented some potential advantage over the intravenous (i.v.) route. Intraperitoneal administration of CPT-11 may be more effective than i.v. administration not only for peritoneal seeding but also for liver metastases. Also, these effects may occur with less toxicity by intraperitoneal administration. Intraperitoneal chemotherapy containing CPT-11 might be an essential option for prevention and treatment of cancerous dissemination of gastrointestinal malignancy [24]

Rate of absorption

Only limited information exists on the rate of transport of drugs out of the peritoneal cavity into the systemic circulation. With the usual injection volumes (0.2–1% of body weight) estimation of the residual fraction in the peritoneal cavity is problematic as recovery of the remaining drug is rather uncertain [18]

Intraosseous drug administration

IO access uses the highly vascularized bone marrow to deliver fluids and medications during cardiopulmonary resuscitation. This route, developed in the 1940s, has been revived In the past decade as a means of achieving rapid vascular access when intravenous access cannot be obtained. The primary advantage of IO access is the high success rate (approximately 80%). Most trained providers can place an IO line within 1–2 minutes. A number of small-scale studies and retrospective reviews have established the usefulness of this route for the delivery of many commonly used resuscitation drugs. In addition, animal models have demonstrated rapid drug delivery to the systemic circulation. While all resuscitation drugs can be given by the IO route, administration of ceftriaxone, chloramphenicol, Phenytoin, tobramycin, and vancomycin may result in lower peak serum concentrations. The most common adverse effect seen with IO use, extravasation, has been reported in 12% of patients. Compartment syndrome, osteomyelitis, and tibial fracture are rare, but have also been reported. [27]

As alternative for drug administration, the intraosseous access is an important option in emergency medicine. Plasma concentrations of drugs, safety and rapidity as well as rate of complications are comparable to the intravenous access. These findings are reflected in the recent resuscitation guidelines, which recommend intraosseous access as an alternative to intravenous access both in children and adults, considering the tracheal route as backup only if the other two options fail. [28]

Intra arterial drug administration

Intra-arterial (IA) injection through the internal carotid artery (ICA) allows for a targeted delivery of therapeutics directly to the brain (Zink, Foley et al. 2009, Guo, Ge et al. 2013). Animal studies using IA injection through the ICA have been combined with an intra-luminal filament middle cerebral artery occlusion (MCAO) surgery model (Guo, Ge et al. 2013, Azedi, Mehrpour et al. 2019). The combination of IA injection and MCAO is a translational approach to mimic drug administration during an endovascular thrombectomy procedure in ischemic stroke patients.

For studies of brain injury, IA injection of compounds through the ICA allows for targeted administration without prior systemic circulation, increasing efficacy. Importantly, IA has a low mortality rate associated with the procedure (Santillan, Rubin et al. 2014). In a mouse study by Maniskas et al., the rate and volume of injection were shown to be important factors for targeted delivery (Maniskas, Bix et al. 2015). They demonstrated how different injection flow rates and volumes through the ICA of mice had either a direct, targeted delivery to the brain or a systemic delivery throughout the body. In rat studies, IA injections have been performed through the ICA (Zink, Foley et al. 2009), femoral artery (Staudacher, Sela et al. 2011), and the subclavian artery (Hayashi, Tomimatsu et al. 2006). However, there have not been any studies aimed at optimizing the injection process itself. Here, we investigated the effects of various flow rates to optimize IA injection through the ICA in male and female rats. When combined with MCAO in future studies, this would allow for optimal delivery of compounds directly to the ischemic region. [29]

Rectal route of drug administration

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