PHARMACEUTICAL PREPARATION AND DRUG DELIVERY

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PHARMACEUTICAL PREPARATION AND DRUG DELIVERY

A Drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals.[1] Drugs intended for human or veterinary use, presented in their finished dosage form. Formulations that have been developed for topical or local delivery or directly administered into the particular region in order to increase bioavailability and improve patient compliance.

The formulations consist of micro or nanoparticles of drug molecules, which may be formed of the drug alone or in combination with an excipient or polymeric carrier. The excipient or polymer may be used to manipulate release rates and to increase adhesion to the affected region. The particular formulation can be applied as a dried powder, a liquid suspension or dispersion, as a topical ointment, cream, lotion, foam, or suppository.

Principles of dosage form design

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations. The excipients provide varied and specialized pharmaceutical functions such as solubilizing, suspending, thickening, preserving, emulsifying, modifying dissolution, and improving compatibility and flavor to the dosage form. Dosage forms can be designed for administration by alternative delivery routes to maximize therapeutic response.

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation that is capable of large-scale manufacture with reproducible product quality.

To ensure product quality, numerous features are required:

1. Chemical and physical stability
2. Uniformity of dose
3. Suitable preservation against microbial contamination
4. Accelerated stability studies
5. Suitable packaging and labeling
6. Acceptability to patients

Ideally, dosage forms should also be independent of patient-to-patient variation. However, in practice, this feature remains difficult to achieve. However, recent developments are beginning to accommodate this requirement. These include drug delivery systems that rely on the specific metabolic activity of individual patients and implants that respond, for example, to externally applied sound or magnetic fields to trigger a drug delivery function. [2]

In recent years, attention has been increased towards eliminating variation in bioavailability characteristics, particularly for medicinal products containing an equivalent dose of a drug substance, as it is recognized that formulation factors can influence their therapeutic performance.

Types of dosage forms

In general, medicines often come in various dosage forms:

Liquid

The active part of the medicine is combined with a liquid to make it easier to take or to have better absorption. A liquid may also be called a mixture, solution, or syrup. Many common liquids are now available without adding any color or sugar.

Tablet

The active ingredient is combined with all other excipients and compressed into a round or oval solid shape. There are different types of tablet dosage forms. In that, soluble or dispersible tablets can safely be dissolved in water.

Capsules

The active part of the medicine is contained inside a gelatin shell that dissolves slowly in the GIT. Gelatin may be of hard gelatin or soft gelatin. Capsules need to be swallowed whole so that the drug in the capsule isn't absorbed until stomach acid breaks down the gelatin shell.

Other types of dosage forms:

Topical medicines

The topical medicines are creams, lotions, or ointments which are applied directly onto the skin. They may come in tubes or bottles depending on the type of medicine.

Suppositories

The active part of the drug is combined with all other ingredients and pressed into a **bullet shape.** So it can be inserted into the bottom. Suppositories mustn't be swallowed.

Drops

These are often used where the active part of the medicine works best if it reaches the affected area directly. They tend to be used for the eye, ear, or nose.

Inhalers

The active part of the medicine is released under pressure directly into the lungs. Young children may need to use a spacer device to take the medicine properly. Inhalers can be difficult to use at first so your pharmacist will show you how to use them.

Injections

There are different types of injection, in how and where they're injected. Subcutaneous injections are given just under the surface of the skin. Intramuscular injections are given into a muscle. Intrathecal injections are given into the fluid around the spinal cord. Intravenous injections are given into a vein.

Implants or patches

These medicines are absorbed through the skin, such as nicotine patches for help in giving up smoking or contraceptive implants.

Buccal or sublingual tablets (Tablet you don't swallow)

These tablets look like normal tablets, but you don't swallow them. Buccal medicines are kept in the cheek so the mouth lining absorbs active ingredients. Sublingual tablets work in the same way but are kept underneath the tongue. Buccal and Sublingual tablets are used only in very specific circumstances.[3]

Drug delivery refers to approaches, formulations, manufacturing techniques, storage systems, and technologies involved in transporting a pharmaceutical compound to its target site to achieve a desired therapeutic effect.[4,5]

Various drug delivery systems are as follows

- Parenteral drug delivery
- Pulmonary drug delivery
- Nasal drug delivery
- Topical and transdermal drug delivery
- Ocular drug delivery
- Rectal and vaginal drug delivery
- Modified release oral drug delivery
- Novel drug delivery
- Magnetically modulated systems.[6]

PARENTERAL DRUG DELIVERY

As per the USP Parenteral drug delivery systems are explained "as those formulations meant for the parenteral route via a primary layer of the body i.e., primary protective skin or additional external boundary tissue, apart from the gastrointestinal tract (GIT)."

MICROBUBBLES AS TARGETED DRUG DELIVERY

The recent advanced methods of non-invasive delivery of therapeutic agents are effective in gene therapy and molecular biology. Besides the well-known application of microbubbles has been demonstrated as an effective technique for the targeted delivery of drugs and genes and is also used as contrast agents for diagnostic ultrasound. The size of microbubbles is larger than a micrometre but smaller than one-hundredth of a millimetre in diameter which is equal to the size of a red blood cell. Because of its smaller size, it can pass in the micro-vessels and capillaries throughout the body. In an aqueous environment, the

microbubbles are unstable and show a surface tension effect. The gas core of microbubbles gets stabilized by lipids, proteins, and polymers.[7,8]

Microbubbles are composed of total particle volume which act as a single chamber so that the shell of the microbubbles separates encapsulated gas and the surrounding aqueous medium by using various shell materials like lipid with thickness ~ 3 nm, protein having 15-20 nm thick and polymer of 100-200 nm thick. Hydrophobic and Vander Waals interactions bind the lipid molecule together and by covalent disulfide bonding the protein molecules get cross-linked so that the formation of bulk-like material.

In water, microbubbles are miniature gas bubbles of less than 50 µ diameter. It mostly contains oxygen or air and remains suspended in the water for an extended period. The gas present in the microbubbles dissolves into the water, and the bubble disappears. Incorporation of a drug in a microbubble includes (1) binding of the drug to the microbubble shell and (2) attachment of the drug at the specific site of the ligand.

In ultrasound-mediated microbubbles, the application of high-intensity ultrasound can rupture capillary blood vessels resulting in the deposit of protein and genetic material into the tissue, and ultrasonic rupture of microvessels with a diameter of 7 µm. Ultrasound forms pores in the membrane of the shell. Ultrasound microbubble causes transient holes in the cell surface resulting in rapid translocation of plasmid DNA from the outside to cytoplasm. Low-intensity ultrasound microbubble (0.6 W/cm^2) caused enhanced drug delivery.[9]

Microbubbles are usually injected intravenously which is a safe process as compared to the use of conventional methods like magnetic resonance imaging and radiography. Microbubble is used in the medical field as diagnostic aids to scan the various organs of the body, and recently they are being proposed to be used as drug or gene carriers and also for treatment in cancer therapy. It is also used to improve the fermentation of soil, to increase the hydroponic plant growth, to increase the aquaculture productivity, and to improve the quality of water, in sewage treatment.

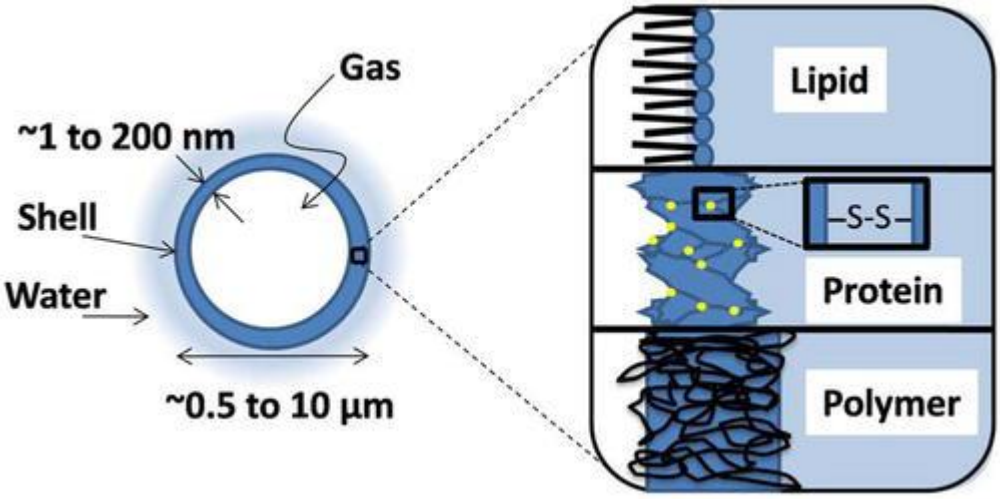


Fig 1. Illustrations describe various shell compositions of microbubbles

The diameter between 0.5 and 10µm is applied for biomedical use so that it can pass through the capillary of the lung.

Composition and physicochemical properties of microbubbles

Protein as a stabilizing agent in the formation of microbubbles

Albumin and several proteins are used to coat microbubbles. The proteins which are amphipathic in nature are highly surface-active. In most of the proteins, the disulfide bridge between two thiol groups is present.[10]

Surfactant as stabilizing agent in the formation of microbubbles

SPAN-40 and TWEEN-40 are used as stabilizing agents in the preparation of microbubbles.[11,12] For the formation of stable microbubbles, the SPAN/TWEEN solution was sonicated in the presence of air.

Lipid as stabilizing agent in the formation of microbubbles

During ultrasound and sonication techniques, the lipid molecules that are held together by weak physical forces form the microbubble shell having the properties of expansion and compression without chain entanglement. Lipid-coated microbubbles therefore reduce the damping effect on resonance and reseal around the gas core during the fragmentation process.[13]

Polymer as a stabilizing agent in the formation of microbubbles

The term "polymer microbubble" typically refers to a special class of microbubbles that are stabilized by a thick shell comprising cross-linked or entangled polymeric species. Polymer shells are most resistant to expansion and compression. During insonification, polymer microbubbles release a gas core which was unstable and rapidly dissolved.

Types of Microbubbles

1. **Perfluorocarbon-filled microbubble:** This is stable for circulating in the vascular system as a blood pool as a carrier.
2. **Ultrasound microbubble:** When applied over the skin surface it bursts and releases the drug. It also increases the therapeutic index. It is advantageous for those drugs which have hazardous and toxic effects.
3. **Albumin-encapsulated microbubble:** which adheres to vessel walls.
4. **Phospholipid-coated microbubble:** Which has a high affinity for chemotherapeutic drugs.[10]

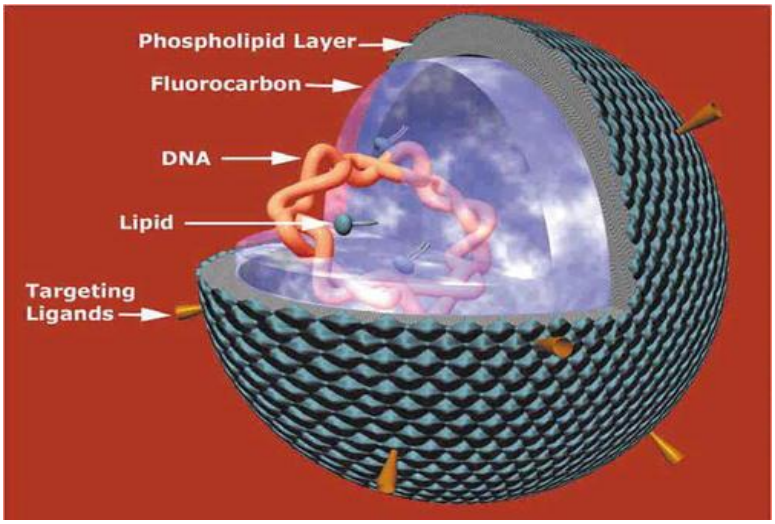


Fig. 2. Perfluorocarbon filled microbubbles

The outer surface is stabilized by amphipathic lipids. Targeting ligands have been incorporated into the head groups of the lipids. The genetic material is stabilized by the cationic lipid. Electron microscopic studies have shown that the DNA is condensed as electron-dense granules within the center of the nanoparticle. The diameter of these particles is about 100-200 nm.[15] There are several advantages to lipid shells. At the air space minimized, the phospholipids hydrophobic acyl chain faces the phospholipids gas, and hydrophilic head groups face the water. Thus the monolayer will form around a newly trained gas bubble. Saturated diacyl phospholipids have very low surface tension below phase transition temperature. This is essential as surface tension at the curved interface induces a place overpressure, thus forcing the gas core to dissolve.[9] The microbubbles stabilize at low tension which is achieved by the lipid monolayer.[16] Monolayers of lipids are highly cohesive and form a solid-like character because of the attractive hydrophobic interaction between the tightly packed acyl chains and Vander Waals.[17] These effects can be effective because the stability of microbubbles during sonication is not dependent on superoxide formation to facilitate disulfide bridging, as in the case of proteins. Therefore, as recent strides described lipids are suitable for a variety of manufacturing techniques apart from sonication.[18]

In the absence of ultrasound, if the adenovirus was administered with microbubbles using the same model, plasmid transgene expression could be directed to the heart, with an even higher specificity than viral vectors, and this expression can be regulated by repeated treatments.[19] Albumin-coated microbubbles significantly improved transgene expression in the skeletal muscle of mice, even in the absence of ultrasound.[20]

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems (TDDS) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects.[21] Evidence of percutaneous drug absorption may be found through the measurable blood levels of the drug, detectable excretion of the drug, its metabolites in the urine, and clinical response of the patients to the therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of the patient's response to drug blood levels. For transdermal drug delivery, it is

considered ideal for the drug to migrate through the skin to the underlying blood supply without build-up in the dermal layers.[22]

Structure of skin

Anatomically, human skin consists of three distinct tissue layers:

- The epidermis
- The dermis
- The subcutaneous fat layer.

Human skin has numerous hair follicles, sweat glands, and sebaceous glands.

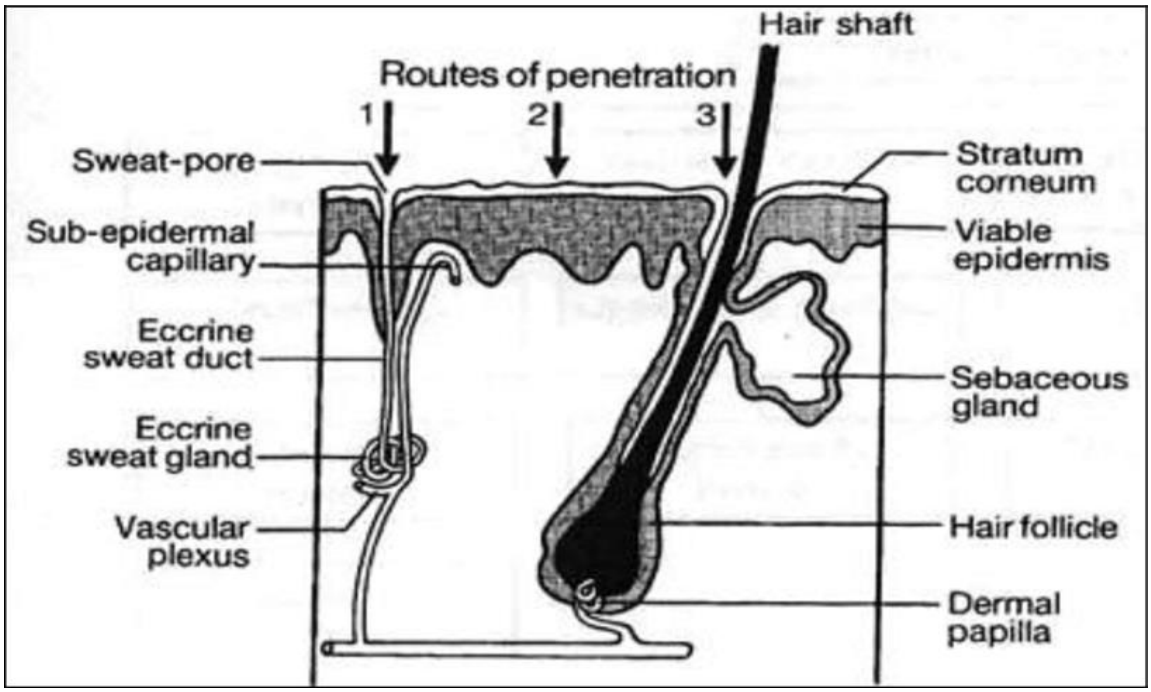


Fig. 3. Structure of skin

The epidermis, the outermost skin layer, consists of stratified squamous epithelial cells. Keratinized, flattened remnants of these actively dividing epidermal cells accumulate at the skin surface as a relatively thin region (about10-20µm thick) termed a stratum corneum or horny layer. The horny layer is itself lamellar with the keratinized cells overlapping one another linked by intercellular bridges and compressed into about 15 layers. The lipid-rich intercellular space in the stratum corneum consists of lamellar matrices with alternating hydrophilic layers and lipophilic bilayers formed during the process of keratinization. The region behaves as a tough but flexible coherent membrane the stratum corneum also is markedly hygroscopic far more so than other keratinous materials, such as hair or nails. The stratum corneum functions as a protective physical and chemical barrier and is only slightly permeable to water. It retards water loss from underlying tissues and minimizes ultraviolet light penetration.

The dermis can be described as a gel structure involving a fibrous protein matrix, embedded in an amorphous, colloidal, ground substance. Blood vessels, lymphatics, and nerves

are found within the dermis. The dermis supports and interacts with the epidermis, facilitating its conformation to underlying muscles and bones.

The subcutaneous fat layer serves as a cushion for the dermis and epidermis. Collagenous fibers from the dermis thread between the accumulations of fat cells, providing a connection between the superficial skin layers and the subcutaneous layer.[23]

Drug travel from dosage form to target

Drug release

Drugs are applied to the skin for treatment of local conditions as liquid and semisolid preparations. These products vary in their polarity and include ointments, liquid and semisolid emulsions (creams), gels, and pastes. Except for paste, all other dosage forms contain a dissolved drug that diffuses from the dosage form into the top layer of the skin. Pastes contain large quantities of undissolved active ingredient that is intended to protect the skin surface and therefore is not released from the dosage form.

Absorption

Most drug absorption occurs through the 0.1μm wide intercellular (paracellular) regions of the stratum corneum. The cells of the stratum corneum, while occupying a greater surface than the intercellular space, are too tightly packed with protein to provide a suitable medium for drug diffusion. Hydration of stratum corneum significantly increases drug absorption by swelling the keratinocytes of the membrane, which loosens the lipid lamellae between the cells. The skin appendages include the hair follicles, the sebaceous glands, and the eccrine glands, extending from the skin surface to the subcutaneous tissue. The ski appendages represent about 0.1% of the total skin surface and their role in the transport of drugs remains unsettled, but it seems likely that these structures make some contribution despite their small surface area due to their thinner layer of stratum corneum. Their role may be limited to the transport of ions, high molecular weight, and hydrophilic drugs. It is estimated that between 0% and 15% of most drugs applied topically are absorbed systemically.

Distribution

Drugs with targets in the viable epidermis or dermis diffuse through the stratum corneum and then partition into the viable epidermis. Drugs move through the viable epidermis primarily by passive diffusion. Normal human keratinocytes have been found to express organic transporting polypeptide carriers and p-glycoprotein. None of the transporters have been characterized in detail. There is evidence that p-glycoprotein has influx transporter activity in the skin, a surprising finding given the skin’s barrier function. The dermis is composed of the structural proteins, collagen, and elastin, suspended in a watery gel of complex carbohydrates. In addition, there are scattered cells in the dermal layer including the fibroblasts that synthesize collagen and elastin macrophages and mast cells that produce allergic and inflammatory reactions in sensory neurons.

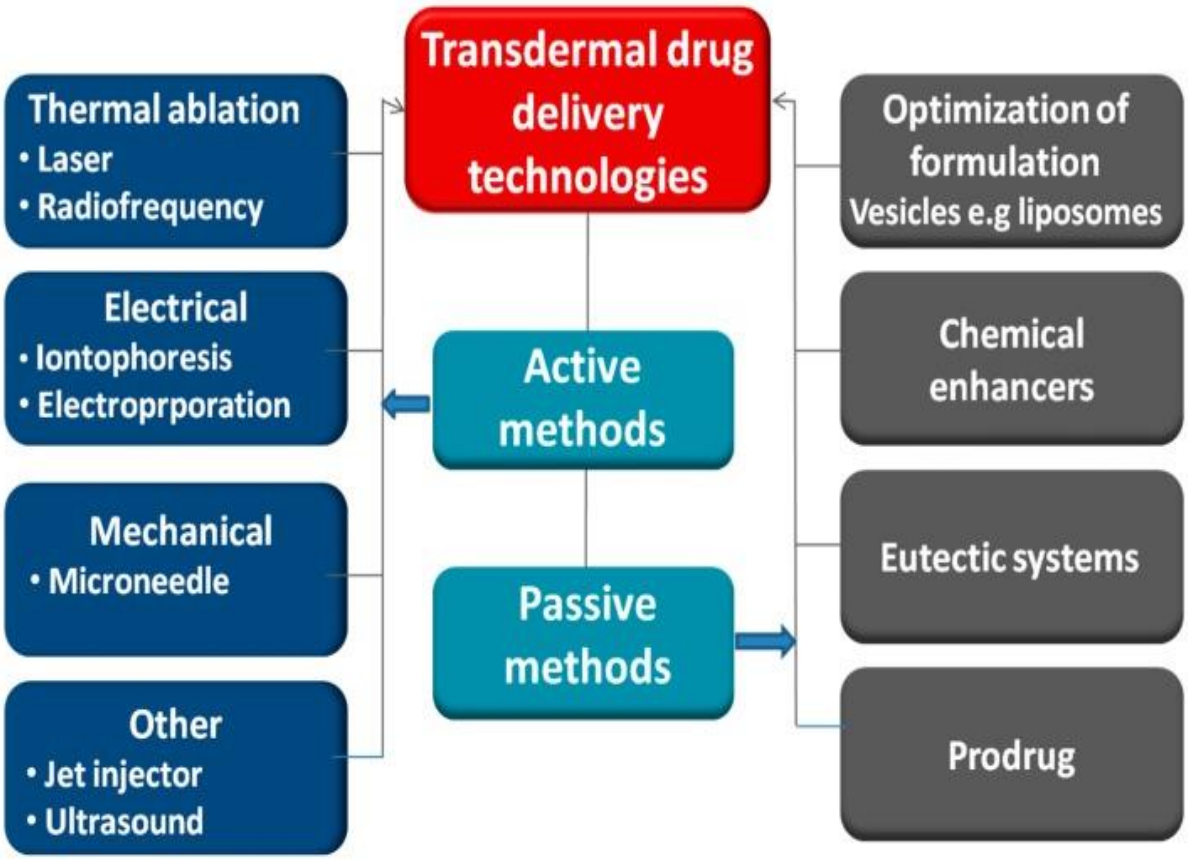
Skin layer Drugs with targets in this layer

- Stratum corneum - Sunscreens, protectants, emollients, keratolytics
- Viable epidermis - Antibiotics, antifungals, antivirals, keratoplasty, depigmenting and pigmenting agents, retinoids, immunosuppressants
- Dermis - Corticosteroids, antihistamines, local anesthetics, Immunosuppressants, drugs applied for systemic action
- Skin appendages - Antibiotics, antifungals, anti-proliferative agents, antiperspirants

SELECTION OF DRUG

For a drug applied to the skin to produce a response at a target in the dermis, the following steps must occur. The drug must be dissolved in the vehicle diffuse through the vehicle to the skin partition into the stratum corneum, diffuse through the stratum corneum, partition into viable epidermis, diffuse through the viable epidermis, partition into dermis diffuse through the dermis.[24]

TECHNIQUES INVOLVED IN TDDS [25]



NASAL DRUG DELIVERY

The nasal route is non-invasive, widely used for local treatment may also be used for systemic therapy as the drug directly goes into systemic circulation. The nasal route gives good absorption of small molecules when compared to large molecules can be increased by absorption promoters. Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal route is an alternative to parenteral therapy and is also useful for long-term therapy.[26]

Intranasal drug delivery is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides.[27] For nasal drug delivery various systems such as nasal spray, nasal pumps, gels, microemulsions, suspensions, powders, and thermos-reversible mucoadhesive gels have been studied.[28]

Factors Influencing Nasal Drug Absorption

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can affect the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity, and the type and characteristics of the selected nasal drug delivery system. The factors influencing nasal drug absorption are described as follows.

1) **Physiochemical properties of the drug**
   Molecular size
   Lipophilic-hydrophilic balance
   Enzymatic degradation in the nasal cavity
2) **Nasal Effect**
   Membrane permeability
   Environmental pH
   Mucociliary clearance
   Cold, rhinitis
3) **Delivery Effect**
   Formulation (Concentration, pH, osmolarity)
   Delivery effects
   Drug distribution and deposition
   Viscosity[29]

Mechanism of Nasal Absorption

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature).[30]So many absorption

mechanisms were established earlier but only two mechanisms have been predominantly used, such as:

A) First mechanism- It involves an aqueous route of transport, which is also known as the para-cellular route but is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

B) Second mechanism- It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate of dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.[31]

Formulation (Concentration, pH, Osmolarity)

The pH of the formulation and nasal surface can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, and is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.[32]

The concentration gradient plays a very important role in the absorption/permeation process of drugs through the nasal membrane due to nasal mucosal damage. Examples of this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.[33]

The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in rats by using a model drug. The sodium chloride concentration of the formulation affects nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to toxicity to the nasal epithelium.[34]

Strategies to Improve Nasal Absorption

Various strategies used to improve the bioavailability of the drug in the nasal mucosa include

- To improve the nasal residence time
- To enhance nasal absorption
- To modify drug structure to change physicochemical properties.

1. Nasal enzyme inhibitors Nasal metabolism of drugs can be eliminated by using enzyme inhibitors. Mainly for the formulation of proteins and peptide molecule development enzyme inhibitors like peptidases and proteases are used.[32] The absorption enhancers like salts and fusidic acid derivatives also show enzyme inhibition activity to increase the absorption and bioavailability of the drug.[33]

2. Permeation enhancers The permeation enhancers are mainly used for the enhancement of absorption of the active medicament. Generally, the absorption enhancers act via one of the following mechanisms:

- Inhibit enzyme activity;
- Reduce mucus viscosity or elasticity;
- Decrease Mucociliary clearance;
- Open tight junctions;
- Solubilize or stabilize the drug.[35]

Nasal Drug Delivery System Dosage Forms

A. Liquid Nasal Formulations

- Instillation and shingle catheter
- Compressed air nebulizers
- Squeezed bottle
- Metered-dose pump spray

B. Powder Dosage Forms

- Insufflators
- Dry powder inhaler:
- Pressurized metered dose inhalers
- Nasal Gels

OCULAR DRUG DELIVERY SYSTEM

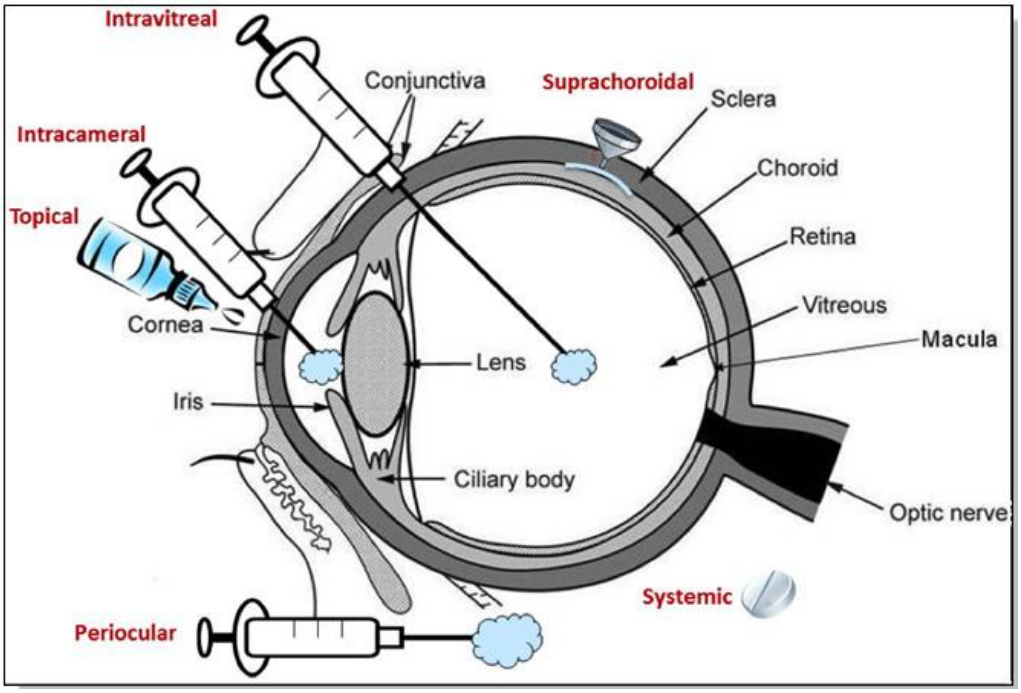
It is the delivery of drugs to the eyes. The preparations which are used to treat diseases in the eyes are called ophthalmic preparations. Ophthalmic preparation, including solutions, suspensions, and ointments can be applied topically to the cornea or instilled in the space between the eyeball and lower eyelid (the cul-de-sac or conjunctival sac of the lower lid).

When drops of an aqueous solution are applied onto the cornea, through which the drug must penetrate to reach the interior part of the eye, the solution in the drops is immediately diluted with tears and washes away rapidly through the lachrymal apparatus.

Consequently, eye drops do not remain in contact with the eye for a long time and they must be administered at relatively frequent intervals.

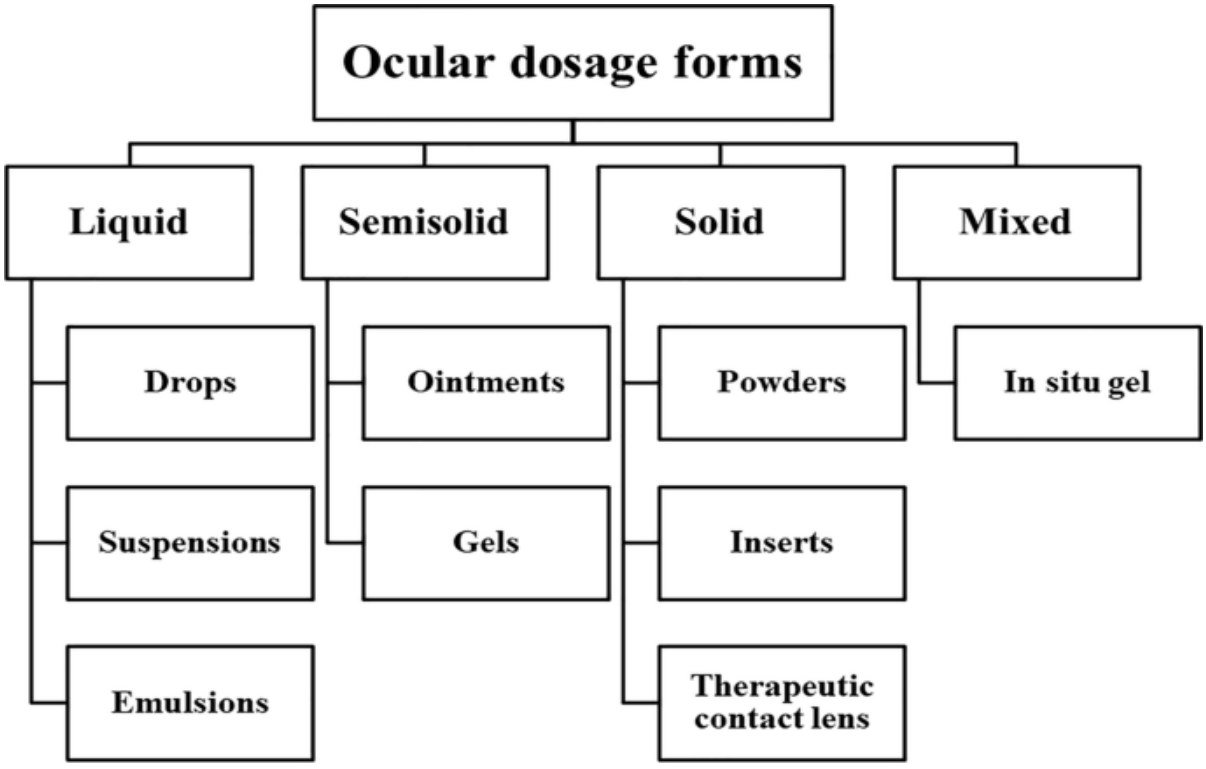
Suspensions have the advantage of longer contact time in the eye, but also the disadvantage of an irritation potential, due to the particle size of the suspended drug.[36]

ANATOMY OF EYE



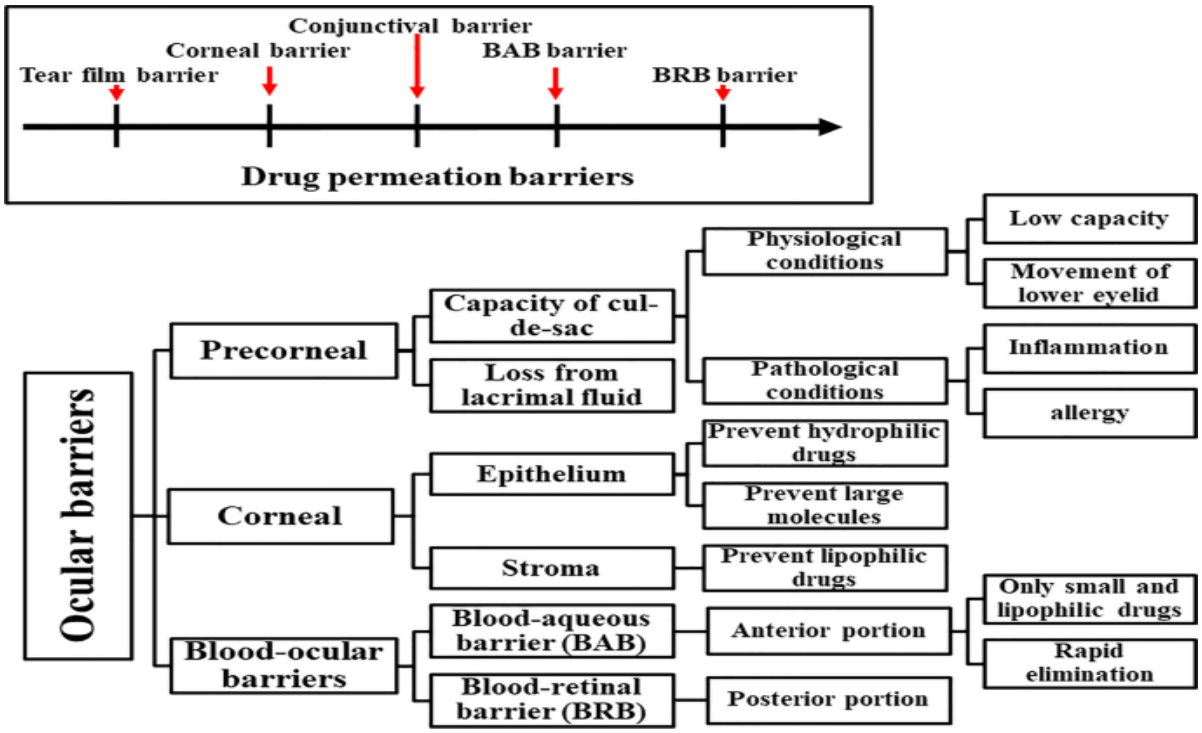
The eye offers multiple entry routes through which ocular drugs may be delivered.[37] Delivery to the anterior segment of the eye may be achieved through topical and sub-conjunctival routes or injected intracamerally. Posterior segment delivery can be achieved topically, systemically, and periocular (I.e., through sub-tenon) via the suprachoroidal space and via intraocular (i.e. intravitreal) injections. The success of therapeutic drug delivery depends on the delivery site, tissue barrier, and pharmacological agent type.[38]

OCULAR DOSAGE FORMS:[40]



Some other novelized ocular drug delivery systems are nano micelles, microneedles, nanosuspensions, liposomes, microcatheters, intravitreal implants, solid corticosteroid implants, and encapsulated hydrogel delivery systems.[39]

Physiological ocular barriers[40]



Routes for ocular drug delivery:

Topical administration is the most common route for ocular drug delivery, representing more than 95% of marketed ocular products. It is the non-invasive route, but with low bioavailability (<5%) due to insufficient corneal permeation and short residence time.[40] Moreover, bioavailability is reduced by tear drainage, blinking, and entering the systemic circulation through the nasolacrimal pathway.

Intracameral Injections

Intracameral injections involve an injection of antibiotics directly into the anterior segment of the eyeball or in the vitreous cavity. Recently, the application of intracameral injection for the treatment of glaucoma using hydrogel functionalized with vinyl sulfone and thiol groups was published. [41]

Intravitreal injections/Implants

Intravitreal injection is a delivery of medicine into the vitreous that is close to the retina at the back of the eye. A new approach for the treatment of glaucoma includes a single intravitreal injection of vitamin E/ poly-lactic-co-glycolic acid microspheres enclosing glial cell line-derived neurotrophic factor, this approach provided a prolonged release for 6 months. Similar results were obtained after intravitreal injection of polymer-free dexamethasone dimer implants.[42] Intravitreal injection of the bio-degradable Rho kinase and protein kinase inhibitor for handling diabetic macular edema and neovascular age-related macular degeneration exhibited prolonged release for about 6 months.[43]

Juxtascleral injections

Juxtascleral injections are used for the treatment of some posterior part complaints that cannot be handled through the conventional topical route. It is used for the treatment of cystoid macula edema, trauma, and diabetic-related conditions. A new approach for the treatment of AMD involves juxta scleral injections of anecortave cortisone that showed prolonged release for 6 months in the choroid and retina.[44] Advanced trans-scleral microneedles have been formulated to carry adeno-associated viruses for retinal gene treatment.[45]

Retrobulbar Injection

The retrobulbar route involves the injection of a needle through the eyelid and orbital fascia to deliver the medication behind the globe into the retrobulbar space. Retrobulbar injection of amphotericin B showed higher antifungal efficacy than intravenous injection.[46] Retrobulbar injection of chlorpromazine is used to manage blind painful eyes.[47] Retrobulbar injection of triamcinolone is utilized to handle macular edema resulting from retinal vein occlusion.[48]

Sub-conjunctival injection

Sub-conjunctival infection is frequently used in cases of very low drug penetration into the anterior part of the eye after topical administration. Significant lowering in corneal inflammation and squamous metaplasia was ensured via sub-conjunctival infection of human mesenchymal stromal cells in mice with graft *versus* host disease.[49]

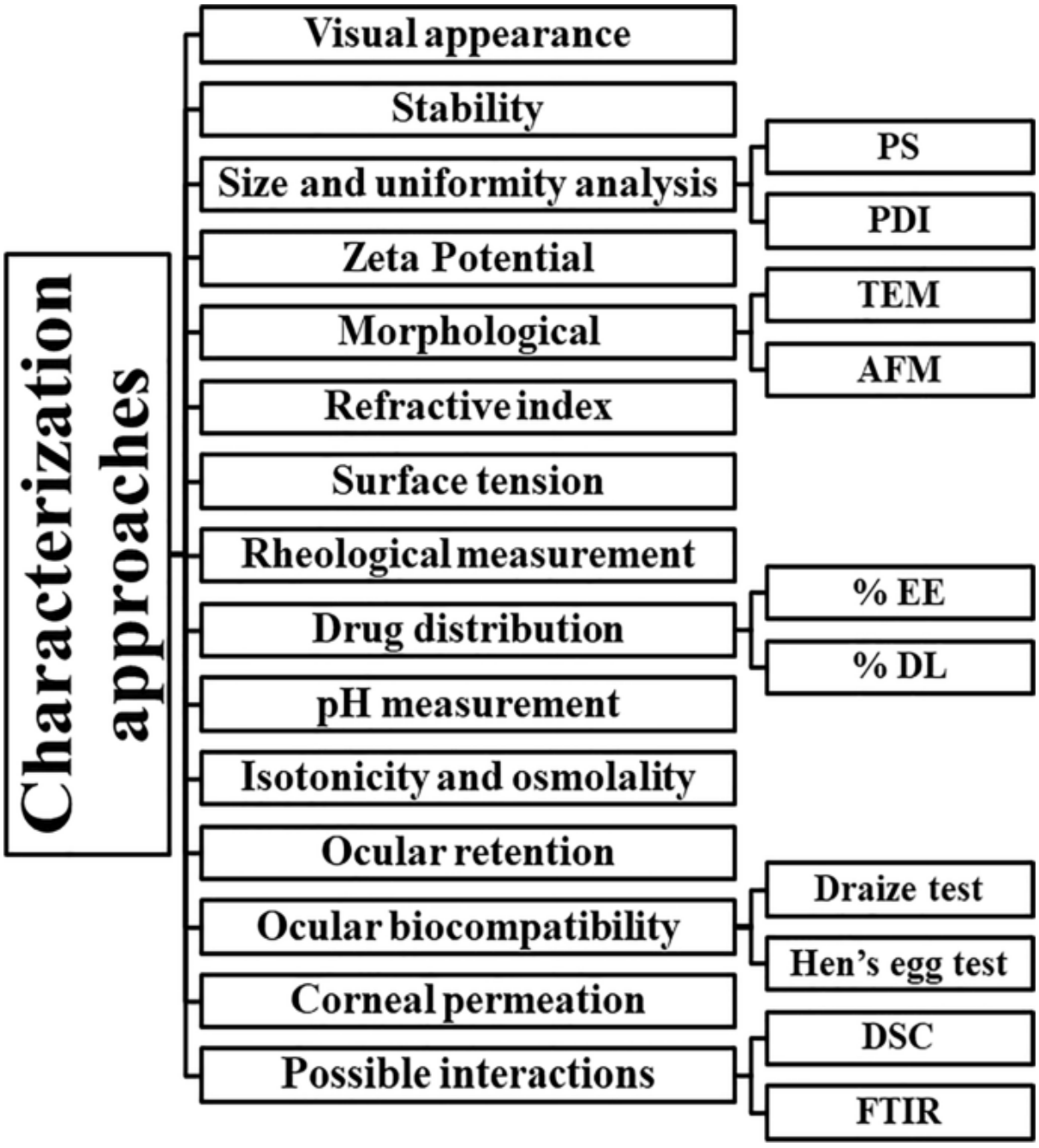
Irrigating solution

They are solutions made under aseptic conditions without the inclusion of preservatives. They are used as balanced salt by surgeons to eradicate blood, and cellular waste and maintain the appropriate hydration volume of the eyes.[50] For example, minimizing the cataract surgical duration and avoiding pupil meiosis by using ketorolac(0.3%w/v) and phenylephrine(1%w/v) in the irrigation solutions.[51]

Iontophoresis

Iontophoresis is a technique used to carry medications into the posterior segment of the eye. It is a technique used to carry medications into the posterior segment of the eye. It involves the usage of voltage gradient. Novel systems involve the employment of micro-needle-based instruments/They had doubled the amount of formula delivered to the back of the eye compared to suprachoroidal injection.[52] The combinations of iontophoretic delivery and contact lens results in 550-1300 times shorter duration than the drug uptake into choroidal capillaries.[53] short-duration iontophoresis of acyclovir prodrug resulted in higher permeation and bioavailability.[54] Ocular iontophoresis of dexamethasone phosphate revealed higher efficacy in managing non-infectious anterior uveitis.[55]

Characterization of Nanocarriers[40]



VAGINAL ADMINISTRATION, INTRAUTERINE AND RECTAL DRUG DELIVERY SYSTEMS

The rectal route is used in many therapies, intended to have either local or systemic effects.

Local action:

For local treatment of pain and itching. Mostly due to the occurrence of hemorrhoids. Locally active drugs include astringents, antiseptics, local anesthetics, vasoconstrictors anti-

inflammatory compounds soothing and protective agents, and some laxatives also all into this category.

Systemic action

All drugs that are orally administered can be given by the route and many are in spite of the limitations discussed above. Antiasthmatic, anti-inflammatory, and analgesic drugs are widely administered by the rectal route. Rectal preparations may also be used for diagnostic purposes.

Absorption of drugs from the rectum is primarily by passive diffusion. Because of inter-individual variations and the venous drainage of the rectum. The bioavailability of drugs following rectal administration is very unpredictable. In general, the rate and extent of drug absorption are lower than the oral route mainly due to the small surface area of oral absorption.

Advantages and limitations of rectal administration

Advantages

- Safe and painless means of administration and removal of the dosage form are usually possible
- Drugs liable to degradation in the gastrointestinal tract can be administered
- Hepatic first-pass elimination of high-clearance drug is partially avoided
- Small and large doses can be administered
- The duration of drug action can be controlled by using a suitable formulation
- Du\rugs can be administered rectally in long-term care of elderly and terminally ill patients
- It is a useful way to administer medication to children unwilling or unable to tolerate the drug orally.
- Administration of rectal suppositories, tablets, or capsules is a simple procedure that can be undertaken by the patient and/or unskilled health care personnel.
- It is useful for patients who are nauseous or vomiting

Limitations

- The patient's acceptability and compliance is poor. Especially for long–term therapy
- Upward movement of the dosage form from the local site can increase first-pass metabolism
- Suppositories can leak
- Insertion of suppositories may be problematic
- Generally, drug absorption from suppositories is slow compared to oral or intravenous administration

Vaginal delivery system

It is in use for estrogen replacement therapy, which when used alone carries the risk of endometrial cancer. Traditionally, this risk is overcome by treatment with progesterone for about 14 to 30 days but it is associated with low oral bioavailability, lack of efficacy, and high level f=of metabolites. Consequently, progesterone tablets, suppositories, and gel have been

developed for vaginal administration. Vaginal administration provides higher and sustained plasma levels and low number of metabolites. Various vaginal preparations of estrogens and progesterone are now available for use as contraceptives, in hormone replacement therapy, and the in-vivo fertilization process.

Physiological factors affecting absorption from the rectum

- Quantity of fluid available
- Properties of rectal mucus
- Contents of the rectum
- Motility of the rectal wall

Rectal and vaginal preparations

Rectal capsules

Rectal capsules (shell suppositories) are solid, single-dose preparations generally similar to capsules. They are oval elongated in shape and have a smooth external appearance that may be lubricated. Capsules used to achieve a systemic effect are usually filled with a solution or suspension of the drug in vegetable oil; or liquid paraffin. There is limited experience with this dosage form, but it seems that no striking differences between the bioavailability of rectal capsules and fatty suppositories.

Rectal tablets

Tablets are not ideal dosage forms because they cannot disintegrate rapidly due to the low amount of water present in the rectum. Rectal tablets releasing CO2 after insertion can be used to stimulate defecation.

Suppositories

As mentioned earlier, suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert localized or systemic drug delivery. Once inserted, the suppository base melts, softens, or dissolves, distributing the medications it carries to the tissues of the region. Suppositories are perfect for their safety, suitability for sustained systemic and local drug delivery, and convenient administration. Progesterone and estrogen vaginal suppositories are available commercially.

Vaginal rings

Vaginal rings containing various progesterone and estrogens are available as steroidal; contraceptives. These rings consist of a drug reservoir surrounded by a polymeric membrane. These are pliable drug delivery systems that can be inserted into the vagina, where they slowly release the drug, which is absorbed into the bloodstream. The most common one is a silastic toroidal-shaped ring, which is about 21/4’’in diameter and the size of the outer rim of a diaphragm, designed for insertion into the vagina and positioned around the cervix for about 21 days.

Levonorgestrel (progesterone alone) is released from the device at a concentration of 20ug/day with nearly a zero-order release. These rings are easy to use with the advantage of reversibility, self-insertion and removal, continuous drug administration at an effective dose level, and better patient compliance. This above device was however associated with irregular

bleeding. Another vaginal silastic silicone ring (Estring) was launched in the united states in 1997 for treating postmenopausal women with symptoms of urogenital aging. The ring provides a constant release (6.5-9.5 µg/day) of estradiol over a 3-month period and gives better results when compared to estradiol-containing pessaries and creams.

Vaginal inserts

Vaginal inserts are in use for prostaglandin delivery. Prostaglandin E2(PGE2) is used to ripen the cervix for induction of labor and for second-trimester abortion. Prostaglandins provide benefits such as reduced time for onset of labor, reduced need for oxytocin, and shortened time for vaginal and cesarean–operated delivery. These inserts are polymeric hydrogel material, which has the ability to absorb fluid and swell without losing its physical form. As it swells, the incorporated drug is released in a controlled manner. An example is the cervical vaginal, which contains 10 mg of dinoprostone and provides release at a rate of 0.3mg/hr in vivo. The retrieval system comprises a Dacron polyester net, which surrounds the insert and has a long ribbon end (net plus ribbon = 31 cm). Another example is the Hycore-V, a hydrogel pessary used to deliver drugs locally via the vagina, and Hycore –R, a rectal delivery system used to deliver drugs systematically. Misoprostol (prostaglandinE1 analog used for terminating second-trimester pregnancy) is also given through the vaginal route at a dose of 100 to 200 µg every 12 hours and provides three times higher bioavailability when compared to oral administration.

INTRAUTERINE DEVICE

An intrauterine device (IUD) is a small plastic device that is placed into the uterine cavity for sustained intrauterine drug release and is usually used for contraception, a typical IUD is shaped like a T and contains a drug usually progesterone in its vertical arm. The progesterone release causes the cervical mucus to become thicker, so sperm cannot reach the egg. It also changes the lining of the uterus so that implantation of a fertilized egg cannot occur. The IUD is inserted through the cervix and placed in the uterus. A small string hangs down from the IUD into the upper part of the vagina and is used to periodically check the device. A shorter-than-normal string can be a warning sign of an embedded IUD.[57]

Quality control of vaginal and rectal dosage forms

Rectal and vaginal dosage forms are evaluated by a set of in-vitro and in-vivo tests of quality and safety as well as effectiveness. These include organoleptic evaluation (color, odor, shape, and surface), release characteristics, melting and solubility, stability, pH, viscosity, spreading, Bio-adhesion, and mechanical strength. some of these are pharmacopoeial requirements and others are carried out during the development phase. A number of these tests will form part of the release and expiry-specific cations of the dosage forms. Formulations are also required to comply with the monograph or the particular dosage form, for example, medicated vaginal tampons must comply with the specific monograph of medicated tampons.

A list of properties that should be controlled

- Appearance
- Weight
- Disintegration

- Melting (dissolution) behaviour
- Mechanical strength
- Content of active ingredient
- Drug release[57]

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