REVIEW ARTICLE

Biological Barriers in Drug Delivery

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Abstract

The concept of biological barriers to drug delivery is crucial for the development and optimization of pharmaceutical treatments. These obstacles represent complex and dynamic physiological systems within the human body that must be navigated by drugs to reach the intended target sites. Key biological barriers include blood-brain barrier (BBB), gastrointestinal (GI) barrier, placental barrier during pregnancy, and immune system. The BBB is a selective interface created by endothelial cells present in the blood arteries of the brain that restricts the flow of many medications, making it difficult to treat neurological illnesses. However, because the medicine comes into contact with different enzymes and transporters in the digestive system, the GI barrier may have an impact on drug absorption and bioavailability. In pregnancy, the placental barrier protects the developing fetus from potential harm, but it can also limit access to the fetal circulation of drugs. While the immune system is primarily responsible for protecting the body from foreign invaders, it can also act as a facilitator and a barrier to drug delivery. Immunotherapies use the immune system to target cancer cells, but the immune response may also lead to drug clearance or side effects. Understanding and addressing these biological barriers is crucial for drug design, formulation, and delivery strategies. Researchers and pharmaceutical companies continue to innovate to optimize drug delivery systems, enabling drugs to overcome these challenges and achieve their intended therapeutic targets effectively and safely. The development of novel drug delivery technologies and strategies promises to provide more precise and effective treatments for a wide range of diseases.

Key words: Barriers, blood-brain barriers, endothelial barriers, mucosal barriers, placental barriers

INTRODUCTION

Biological barriers are important in medication delivery because they influence the efficacy of pharmacological drugs in reaching their intended targets within the human body. These barriers are a complex network of natural defensive systems that evolved over time to defend the body against outside chemicals and diseases. The complex interaction of numerous biological barriers, such as the gastrointestinal (GI) tract, blood-brain barrier (BBB), and skin, poses substantial obstacles in the design and implementation of drug delivery systems.[1] Overcoming these hurdles is critical to ensure that medications are delivered quickly and securely to their intended areas of action, boosting therapeutic potential while reducing adverse effects. There are some barriers which are involved in drug delivery:

The BBB

The BBB is a specialized structure generated by the intimate interaction of endothelial cells that line blood arteries in the brain with other supportive cells such as astrocytes and pericytes. This barrier is largely found in the brain's microvasculature, where it acts as a gatekeeper, rigorously regulating the movement of chemicals and cells between the circulation and brain tissue.[2]

Mucosal barriers

Mucus lines mucosal surfaces, such as those in the GI, and respiratory systems, acting as a protective barrier. Because mucus can trap and hinder drug absorption, specific formulations for effective mucosal drug delivery are required.[3]

Endothelial barriers

The endothelial cells that line blood arteries have tight connections that prevent medicines from passing

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Received: 20-02-2024
Revised: 13-05-2024
Accepted: 28-05-2024

uncontrollably into tissues. While this barrier is necessary for tissue homeostasis, it can impede therapeutic delivery to target areas.

Cell membranes and membrane transporters

Once medications have passed through the endothelial barrier, they face further challenges within cells. Drug absorption and distribution within target cells can be hampered by cellular membranes and membrane transporters.

Skin barriers

The skin barrier is the human body's initial line of defense, acting as a strong barrier against outside threats. The epidermis, or outermost layer of the skin, is made up of densely packed keratinocytes that are strengthened by natural oils, perspiration, and hair.[4] These physical and chemical components combine to form an impenetrable barrier that keeps bacteria and hazardous chemicals at bay. Langerhans cells are immune cells found in the skin that are strategically placed to detect and respond to potential intruders. Furthermore, melanin production in the skin defends against the harmful effects of ultraviolet radiation. All things considered, the skin barrier is a sophisticated and significant defensive mechanism that is critical to general health and well-being.

Immune system

The immune system can be a significant barrier to pharmaceutical administration, thereby influencing treatment efficacy and safety. When foreign compounds, including drugs, enter the body, the immune system recognizes them as potential[5] threats and responds accordingly. This detection may result in immunological responses such as immune cell activation or antibody production, leading to rapid clearance and destruction of the drug. This may make it more difficult for the treatment to reach its target and exert its therapeutic effects. To get over this barrier, scientists have developed a number of ways, such as encapsulating drugs in nanoparticles or liposomes, which can help evade immune detection and extend the drug's circulation length. Understanding and controlling the interplay between the immune system and medicine administration is critical for improving the effectiveness and precision of medical therapy [Figures 1 and 2].

Excretory barrier

The excretory system of the human body is an important barrier for getting rid of extraneous material and waste [Figure 3]. It consists of organs such as the kidneys, bladder, and,[6] urinary tract. Its job is to eliminate metabolic waste, toxins, and excess materials from the circulation, such as urea, creatinine, and excessive salt [Figure 4]. The excretory system is critical to maintaining the body's internal balance since waste items can become hazardous if they accumulate. It supports to overall health and homeostasis by properly eliminating waste and retaining critical nutrients through filtration, reabsorption, and secretion.

Placental barrier

During pregnancy, humans form the placental barrier, which is a unique and critical physiological structure. It serves as a barrier that is selective between the circulatory systems of the mother and the fetus, allowing waste products, nutrients, and oxygen to be exchanged but preventing blood from directly mingling. The placenta, a transitory organ that develops in the uterus during pregnancy, is the main component that forms this barrier. The placental barrier[7] allows critical molecules, such as oxygen and nutrition, to be transferred from the mother to the developing baby while protecting it from hazardous substances contained in the mother's blood, such as toxins and diseases. It is essential for maintaining the growing baby's health and growth, and any interference or malfunction in this barrier can have serious consequences for the health of the developing fetus.

Understanding the complexities of these biological barriers is critical for drug developers because it allows them to build drug delivery methods that can skip, breach, or exploit these natural defensive mechanisms. This enhances pharmaceutical therapy's effectiveness and safety. Overcoming biological barriers is a fast-changing field of research, with new technologies and approaches being developed all the time to overcome these impediments and enable more effective and personalized medication delivery. This review article will delve deeper into the different biological barriers encountered in medicine administration and the strategies employed to successfully overcome these barriers, therefore opening up new avenues for improved patient care and therapeutic outcomes.

BBB

The BBB is a complex physiological barrier that separates circulation from the brain and central nervous system (CNS). The BBB is a structure composed of specialized endothelial cells, tight junctions, and astrocytes that serve as a potent defense mechanism that regulates chemical transit into and out of the brain.

Tight junctions between endothelial cells in brain capillaries constitute a physical barrier that prevents uncontrolled chemical flow. This barrier selectively permits critical nutrients such as amino acids and glucose into the brain while limiting potentially harmful chemicals such as toxins and viruses. Tight junctions also prevent most medications from entering the body, making it difficult to administer therapeutic agents

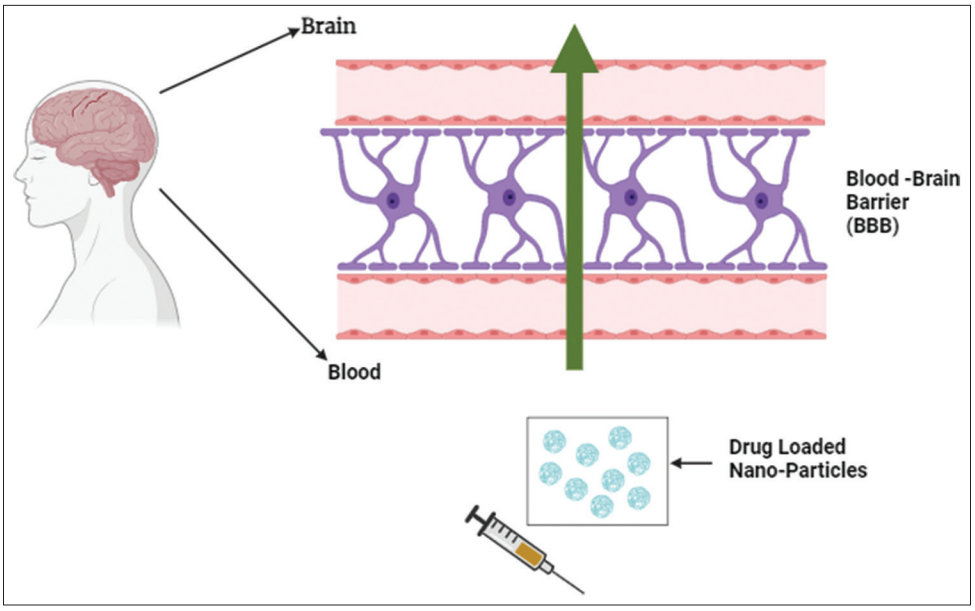


Figure 1: Blood-brain barrier

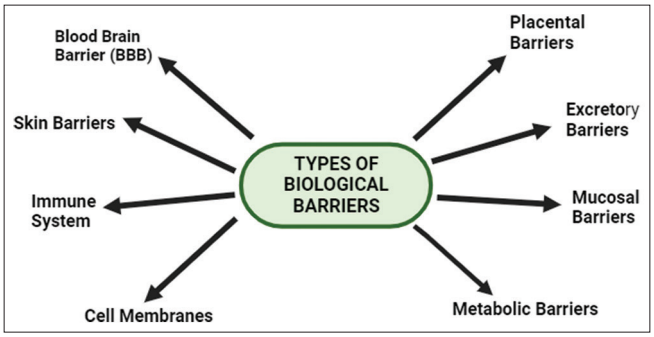


Figure 2: Types of biological barriers

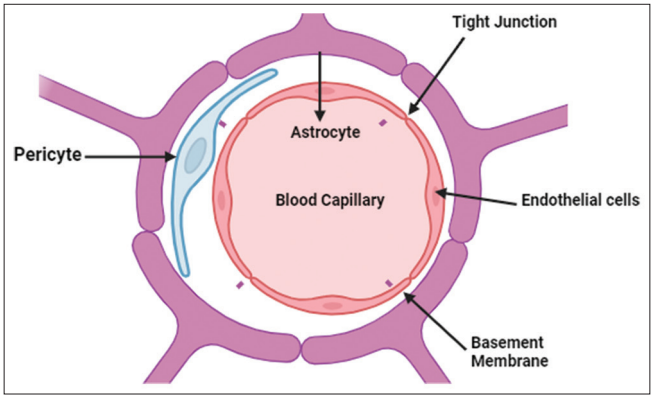


Figure 3: Components of blood-brain barrier

for treating neurological diseases. The existence of efflux transporters in the BBB complicates matters further since they actively release medicines into the brain.[8] This phenomenon may significantly reduce the concentration of drugs available for the intended therapeutic effects. While the BBB protects the brain from damage, it is a major obstacle to the development of drugs for neurological disorders. Researchers are continuing to investigate novel drug delivery strategies, such as nanoparticles

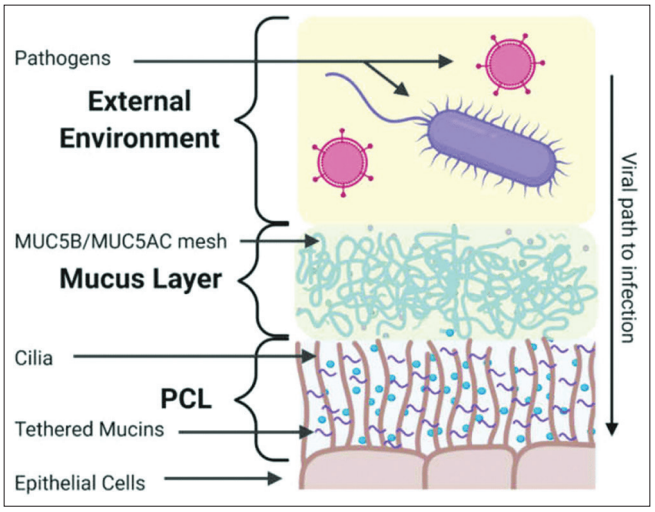


Figure 4: Mucosal barrier

and receptor-mediated transport (RMMT), to selectively and safely breach the BBB and improve medicine administration for diseases such as Parkinson's and Alzheimer's, as well as brain malignancies. Understanding and manipulating the physiology of the BBB is crucial for the advancement of neuropharmacological treatments [Figure 5].

The BBB, also known as the BBB, separates the circulation from the brain and CNS. It regulates the transport of chemicals,[9] including medications, from the blood to the brain. The BBB mechanism in medication transport incorporates many critical aspects [Figure 6]:

Tight junctions

Tight junctions join endothelial cells that line capillaries in the brain. These junctions establish a physical barrier

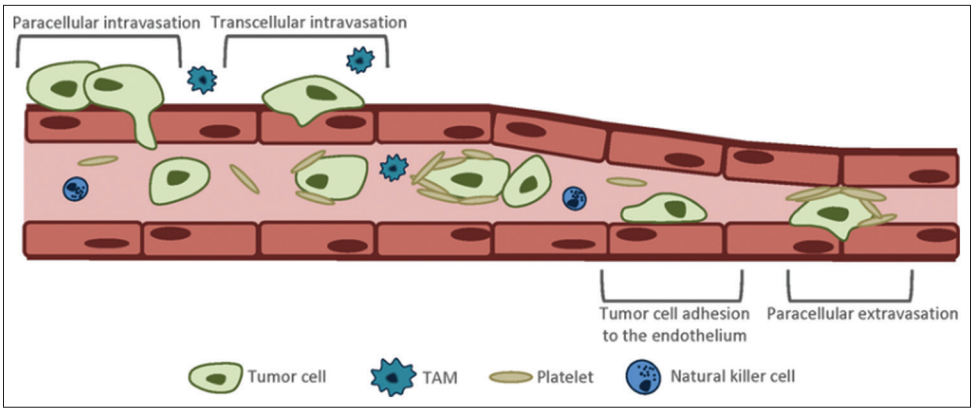


Figure 5: Endothelial barrier

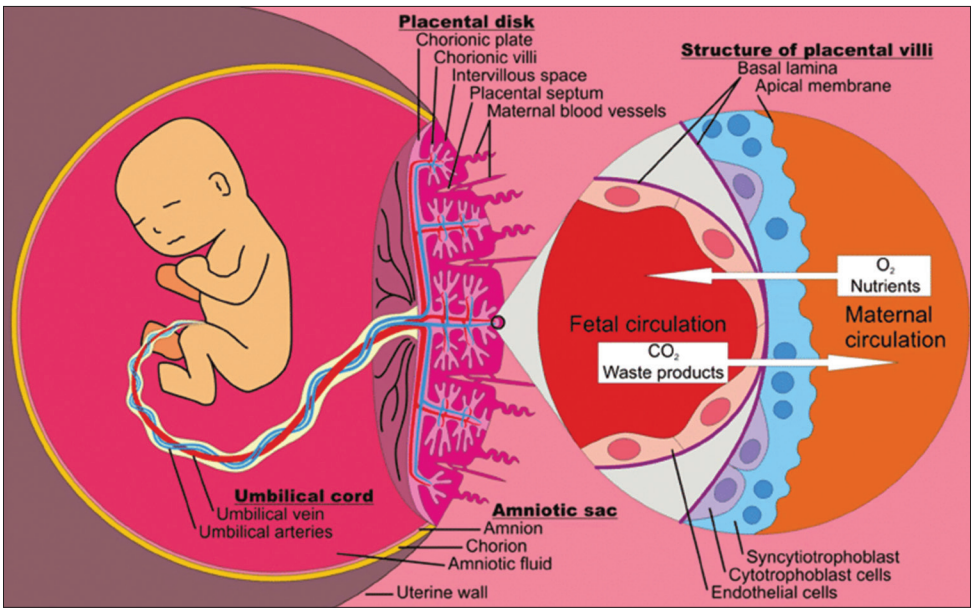


Figure 6: Placental barrier

that prevents most substances, including medications, from moving from the circulation into the brain. This selective permeability keeps potentially dangerous chemicals out of the brain.

Efflux transporters

The BBB contains efflux transporters that actively pump out medicines that penetrate the layers of endothelial cells and reach the brain. This efflux mechanism[10] can significantly reduce the concentration of drugs intended for therapeutic effects [Table 1].

Limited passive diffusion

Due to the tight connections and lipid-rich environment of the cell membrane, medicines cannot easily passively diffuse across the BBB, as they may in many other tissues.

Specialized transport systems

To promote the movement of critical nutrients and molecules, the BBB features unique transport channels for amino acids, glucose, proteins, and other necessary chemicals. The utilization of these transport mechanisms for medication delivery through these channels has been examined.

RMMT

Certain chemicals, such as insulin, can penetrate the BBB through receptor-mediated endocytosis. Similar receptor-mediated pathways can be used to transport therapeutic substances across the BBB in drug delivery techniques [Table 2].

The objective of drug delivery to the brain is to create systems that can successfully administer therapeutic drugs by bypassing or across the BBB [Table 4]. This might involve modifying

Table 1: Route of administration and examples of drugs that can pass through mucosal barrier

S. No.	Drug class	Route of administration	Example of drugs
1	Oral	Oral	Aspirin, paracetamol, antibiotics
2	Nasal	Nasal spray or drops	Decongestants, Nasal steroids
3	Buccal	Between cheek and gum	Nicotine, Certain pain medications
4	Sublingual	Under the tongue	Nitroglycerin, sublingual allergen immunotherapy tablets
5	Rectal	Rectal suppository	Acetaminophen
6	Vaginal	Vaginal suppository or gel	Antifungals, hormonal contraceptives
7	Ocular	Ophthalmic drops	Antibiotics, glaucoma medications
8	Inhalation	Pulmonary inhaler	Bronchodilators, inhaled corticosteroids
9	Transdermal	Skin Patch	Nicotine, fentanyl

Table 2: Drugs that can pass through cell membranes and membrane transporters

S. No.	Drug category	Examples	Mechanisms
1	Opioid analgesics	Morphine, Oxycodone	Binds to opioid receptors in neurons.
2	Anti-diabetic drugs	Metformin, Sulfonylurea	Affects glucose transport and metabolism
3	Diuretics	Hydrochlorothiazide, Furosemide	Influence ion transport in renal tubules
4	Cardiovascular drugs	Propranolol (Beta-Blocker), Verapamil (Calcium channel blocker)	Target receptors in cardiovascular cells
5	Anti-psychotic drugs	Haloperidol (Typical), Risperidone (Atypical)	Interact with various neurotransmitter receptors
6	Antidepressants	Fluoxetine, Amitriptyline	Act on neurotransmitter receptor inside neuron
7	Antibiotics	Amoxicillin, Erythromycin	Penetrate bacterial cell membranes
8	Antiviral drugs	Acyclovir, Tenofovir	Target intracellular viral components
9	Lipophilc drugs	Diazepam (Benzodiazepine), Ibuprofen (NSAIDs)	Diffuse passively through lipid bilayers
10	Small molecule drugs	Aspirin, Paracetamol	Can penetrate cell membranes through diffusion
11	Anti-cancer drugs	Doxorubicin, Cisplatin	Enter cells and interact with intracellular targets

medication formulations to boost lipophilicity, employing nanotechnology, or developing drug carriers capable of utilizing specialized transport mechanisms and receptors at the BBB. Another possibility for enhancing medicine delivery to the brain while keeping the security and integrity of the BBB is the identification of pharmaceuticals that are more permeable to the BBB or treating illnesses through different channels, such as intracerebroventricular injection. Understanding the complicated mechanics of the BBB is crucial for developing therapeutics for a wide range of neurological diseases.

The BBB, also known as the BBB, is a highly specific barrier that prevents many chemicals from entering the brain from the circulation. Some medications, on the other hand, are designed or have qualities that allow them to pass through the BBB and reach their intended targets in the CNS.[11] The following are some examples of medications that can cross the BBB:

Lipophilic medications

Lipider substances that are lipid-soluble or have a high lipophilicity[12] can easily cross the BBB. This is because the BBB cellular membranes are mostly made up of lipids. Some examples include anesthetics, sedatives, and psychotropic compounds.

Tiny molecules

Drugs having a molecule with a low and a tiny size are more likely to penetrate the BBB. This category includes a vast range of neuroactive pharmaceuticals, such as anti-seizure medications.

Active transport

Some medications enter the brain through particular transport systems. Glucose, for example, is carried into the brain through glucose transporters. Researchers are investigating ways for developing medications that mirror the organization of endogenous molecules[13] carried into the brain, allowing them to take advantage of these transport networks.

Table 3: Description and challenges of biological barriers in drug delivery

S. No.	Biological barrier	Description	Challenges in drug delivery
1.	GI barrier	The barrier in the digestive tract that includes stomach acidity, enzymatic degradation, and mucosal lining	Drug degradation, Poor oral bioavailability
2.	Blood-brain barrier	A protective barrier separating the bloodstream from the brain. Composed of tight junction and efflux transporters.	Limited drug access to the central nervous system
3.	Skin barrier	Multiple layers of skin that restrict drug absorption.	Transdermal delivery system required for skin penetration
4.	Mucosal barriers	Barriers in the respiratory, GI, and genitourinary tracts, including mucus layers and enzymatic degradation.	Challenges in drug delivery to mucosal tissues
5.	Immune system	Immune recognition and clearance of foreign substances, including drugs	Development of immunomodulatory drug carriers
6.	Metabolic Barriers	Enzymatic metabolism of drugs in the body.	Prodrugs and drug formulations to resist metabolism
7.	Excretory Barriers	Removal of drugs through kidneys and liver.	Strategies to prolong drug circulation in the bloodstream
8.	Cell Membranes	Transport of drugs across cell membranes to reach intracellular targets.	Lipophilic drugs and transporter proteins' roles
9.	Placental Barrier	Regulates drug transfer from the mother to the developing fetus during pregnancy.	Safety concerns when administering drugs during pregnancy.

Prodrugs

Prodrugs are inert chemicals that are converted by the body into active drugs. A medication delivery technique is to design prodrugs with features that allow them to cross the BBB's barrier and then be transformed to their active forms within the brain.

Nanoparticles

Drugs can be carried across the BBB using nanoparticles. These nanoparticles may be coated or engineered in such a manner that they may escape the BBB's tight connections or be actively carried over.

RMMT

Some medications can be tailored to target specific BBB receptors, allowing them to enter the brain more easily. This method is being investigated in the development of tailored medicines for a variety of neurological diseases.[14]

Intracerebroventricular administration

For some medications that have difficulties crossing the BBB, direct delivery into the cerebrospinal fluid (intracerebroventricular administration) may be investigated. As a result, it is given straight to the CNS.

However, while certain medications may cross the BBB, this does not ensure their effectiveness or safety. The transit of the BBB can be complicated, and parameters such as medication concentration, protein binding, and potential adverse effects must be carefully examined. Developing medicines that penetrate the BBB while retaining therapeutic efficacy and limiting side effects is a serious problem in neuropharmacology.

The BBB serves as a protective barrier between the circulation and the brain and CNS. It is mostly found in the brain and spinal cord microvasculature. The BBB is not a solid wall, but rather a dynamic and highly selective interface that carefully restricts the movement of chemicals from the circulation into brain tissue.

The following are the key BBB components:

a. Endothelial Cells: Tight connections connect specialized endothelial cells that comprise the inner lining of brain capillaries. A variety of chemicals, including medications and poisons, find it difficult to pass past the endothelial cell layer due to these tight connections.
b. Astrocytes are star-shaped cells that surround the brain's blood arteries. These cells are critical in maintaining the BBB's integrity and function. It connects with endothelial cells and aids in the regulation of molecule flow.
c. Basement Membrane: Located underneath the endothelial cells, the basement membrane offers structural support and aids in the regulation of substance transport.
d. Pericytes: These cells are found near to endothelial cells and play a crucial role in blood flow control and BBB integrity.

The BBB's primary role is to shield the brain and spinal cord from dangerous chemicals while allowing important nutrients and molecules to flow through. Selective permeability is critical for preserving the stable and regulated environment required for normal brain function.

The BBB is an important component of the CNS because it protects the brain from toxins and viruses in the circulation, preserving appropriate brain function and health.

MUCOSAL BARRIER

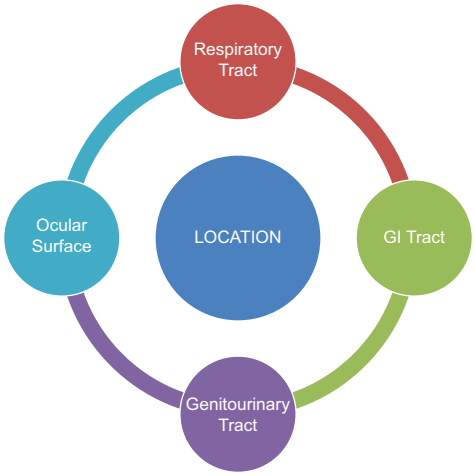
The mucosal barrier is an important element of the immune system that protects the human body from pathogens including bacteria, viruses, and other potentially harmful substances.[15] The mucous membrane immune system or mucosal defense system is another name for it. It is largely made up of mucous membranes, which line many different sections of the body. The mucosal barrier is described in detail below:

Mucous membranes are mucosal barriers that protect the inside surfaces of several organs and compartments in the human body. Membranes protect the digestive tract, as well as the oral and nasal airways. It has an impact on both the airways and the urogenital tract. The mucosal barrier is composed of several layers of epithelial cells. These cells are closely packed together, producing a protective barrier. The mucous membrane secretes mucus, which adds another layer of protection.

Functions

1. Physical Barrier: It restricts the entry of viruses and poisons into the body.
2. Immune Defense: It contains immune cells which detect and fight with infections.
3. Germ Destruction: To trap and destroy germs, mucous membranes secrete mucus and other antibacterial compounds.
4. By distinguishing between hazardous and innocuous microorganisms, the mucosal immune system establishes tolerance and allergies.
5. Mucosal Barrier Interaction: The mucosal barrier interacts with helpful bacteria in the human body.
6. The mucosal barrier can be harmed by allergies, infections, autoimmune diseases, and inflammatory disorders.

Mucosal barriers are found all over the body and serve as the first line of defense against pathogens and foreign substances. These barriers are covered with mucous membranes that secrete mucus to trap and expel the invaders. Here are the key locations of mucosal barriers in the human body:



Respiratory tract

In respiratory tract, nasal mucosa contains mucus membrane that helps to filter and humidify the air and it also present in the lower respiratory tract to remove inhaled pathogens and small particles.

GI tract

In the GI tract, mucus membrane is present. It present specially in oral cavity, esophagus, stomach, and intestine. In esophagus, esophagial mucus protects from harmful substances and bacteria, and in the stomach and intestinal area it defends against ingested pathogens.

Genitourinary tract

In genitourinary tract, vaginal mucosa protects against infections in women and urethral mucosa prevents from urinary tract infection.

Ocular surface

In ocular surface, conjunctiva is present, it covers the front of the eye and inner eyelids.

Many medications are intended to overcome mucosal barriers to be absorbed properly into the circulation. These medications can be delivered by oral, nasal, buccal (between the cheek and mouth), sublingual (under the tongue), rectal, vaginal, ophthalmic, and even pulmonary (inhalation) methods.[16] A drug's capacity to pass a particular mucosal barrier is determined by its physicochemical qualities, formulation, and intended route of administration. A simplified table detailing various medications and their usual methods of delivery over mucosal barriers is provided below:

Please keep in mind that the effectiveness and safety of different routes of drug absorption might vary greatly

depending on the medicine's exact formulation, therefore it is critical to use the prescription or suggested administration strategy for each medication. Furthermore, due to variables such as drug degradation, first-pass metabolism, or mucosal membrane permeability, some medications may have restricted bioavailability when taken through specific mucosal routes.

ENDOTHELIAL BARRIERS

Endothelial barriers protect blood arteries by controlling the complicated chemical flux between circulations and surrounding tissues. Endothelial cells are responsible for the smooth lining of blood arteries, capillaries, and lymphatic channels.[17] It is capable of wide range of tasks including feeding and oxygen transport to tissue and also it prevents from dangerous diseases and toxins by restrict their entry into circulation. The integrity of the endothelium barrier is critical for vascular homeostasis and overall health because any disruption it may cause health disorders such as inflammation, water retention, and cardiovascular disease.

Endothelial barriers are found in blood vessels, capillaries, lymphatic vessels, heart, brain, lungs, and kidneys. In blood vessels, they are present in walls of arteries and veins.

Capillaries

Endothelial barriers are present in the capillaries. Capillaries are the tiniest blood vessels and are largely made up of endothelial cells.

Lymphatic vessels

Endothelial cells are present in lymphatic vessels which are necessary for immunological function and fluid balance in the body.

Brain

BBB is present in the brain which is made up by endothelial cells that are responsible for chemical flow into and out of the brain.

Lungs

The lungs' pulmonary capillaries allow oxygen and carbon dioxide to exchange while breathing.

Kidneys

Renal endothelial cells are involved in blood filtration and urine generation in the kidneys.

Drugs that can cross the endothelium barrier, commonly known as the BBB or other comparable barriers in the body, have unique properties that allow them to pass through these protective layers. These qualities are typically:

Lipophilic (fat-soluble) drugs

They can more easily traverse the endothelium barrier because cell membranes, particularly those of endothelial cells, are predominantly constituted of lipids. Lipophilic medicines can dissolve in these membranes' lipid bilayers.

Low molecular weight

Smaller molecules diffuse more easily past the endothelium barrier. Due to their size and incapacity to negotiate the tight connections between endothelial cells, large molecules frequently struggle to permeate.

Non-ionized form

Drugs that are non-ionized or uncharged are more permeable across the endothelium barrier. This is due to the difficulties charged molecules have in moving across lipid membranes.

Active transport

Some medications can use particular transport proteins or carriers to go past the barrier. Drugs can be transported from the circulation into surrounding tissues, including the brain in the case of the BBB.

Prodrug conversions

In certain circumstances, inactive prodrugs are provided until they are converted into an active form that can penetrate the barrier more efficiently.

Disruption of the barrier

To allow medicine entrance, the barrier can be temporarily disrupted using methods such as focused ultrasound or hyperosmotic agents in specific instances. This is utilized in medical operations to get over a barrier for certain treatments.

It is crucial to note that not all medications can easily penetrate the endothelium barrier, and this trait is critical when creating pharmaceuticals for disorders that necessitate treatments reaching particular parts of the body, such as the CNS. When targeting the brain or other protected areas, researchers and pharmaceutical firms create medications with these properties in mind to enhance efficacy and safety.

CELL MEMBRANES AND MEMBRANE TRANSPORTERS

The efficacy and success of medication delivery to target cells and tissues are heavily reliant on cell membranes and membrane transporters. These elements serve as barriers by regulating the entry and exit of substances, including medications, into and out of cells. Here's how cell membranes and membrane transporters act as medication delivery barriers:

Selective permeability

Cell membranes are selectively permeable, which means that certain molecules can flow through while others cannot. The existence of diverse types of membrane proteins, such as transporters and channels, accounts for this selectivity.[18] Drugs must be able to pass through or interact with these proteins to enter cells. Many medications are intended to enter cells by utilizing specialized transporters or channels. However, not all drugs can easily do so.

Active transport

In some circumstances, medications must be actively delivered into cells against their concentration gradient. This process takes energy and includes active transporters, which are transport proteins. Active transporters can limit or boost drug absorption[19] dependent on their existence and activity, making them both a barrier and a facilitator in drug delivery.

Efflux transporters

Efflux transporters are proteins that actively pump medicines out of cells. This can develop to medication resistance, limiting therapy efficacy. Overexpression of efflux transporters, such as P-glycoprotein, can restrict drug accumulation within target cells, reducing therapeutic efficacy.

Membrane potential

It can influence medication delivery. Some medications are charged molecules, and depending on their charge and the direction of the potential, the membrane potential can either promote or impede their entrance into the cell.

Size and hydrophobicity

Drug physical properties, such as size and hydrophobicity, can impact their ability to cross the cell membrane. Small, lipophilic compounds can diffuse across the lipid bilayer, but bigger, hydrophilic medications may have more difficulty traversing the membrane.

Receptor-mediated endocytosis

Some medications are engineered to bind to specific receptors on the cell surface, allowing them to enter the body through endocytosis. While this can be a drug absorption route, it also has limitations in terms of receptor availability, specificity, and endocytic processes.

To overcome these barriers and improve drug delivery, pharmaceutical scientists create drug formulations that optimize drug properties for cell membrane interactions, investigate the use of prodrugs or nanocarriers that improve cell penetration, and create drugs that target specific membrane receptors or transporters. Understanding how cell membranes and membrane transporters interact is critical for developing successful medication delivery techniques.

Cell membranes are found in all types of cells and act as a protective barrier between the cell's interior and its external environment. Cell membranes are found within the cells, enclosing the cytoplasm and organelles.[20] They are primarily composed of a lipid bilayer packed with various proteins that govern the passage of substances into and out of the cell. These membranes operate as barriers in drug delivery because they may selectively allow or restrict the entry of medications and other molecules, which can have a substantial impact on drug delivery efficacy.

Membrane transporters are proteins present in or on the cell membrane that govern the movement of numerous substances, including[21] medicines. These transporters are required for the transfer of chemicals into and out of cells. Membrane transporters' locations vary depending on the transporter, since they may be found in many cell types and tissues, with some being more numerous in certain organs. The existence and function of certain membrane transporters can have a significant impact on drug absorption, distribution, and elimination in the body. Understanding the location and function of these transporters is critical in drug development because they may either help or impede drug delivery to their intended targets, influencing therapeutic effectiveness and possible adverse effects. These transporters are often studied by researchers and pharmaceutical firms to build drug delivery methods that can overcome these obstacles and increase medication bioavailability.

Remember that these examples include a variety of drug categories and modes of action. A drug's capacity to cross cell membranes and interact with membrane transporters varies depending on its chemical structure and the individual transporters involved. Pharmaceutical research and development focuses on improving medicinal qualities to increase effectiveness while minimizing potential negative effects. The precise pharmaceuticals used for treatment are determined by the illness being treated, and healthcare experts take a variety of factors into account when prescribing medications to patients.

SKIN BARRIER

The skin barrier, which covers and shields the skin's outer surface, is present throughout the whole body. The main chemical and physical defense against outside hazards is provided by the skin's outermost layer or epidermis. The skin is the body's most apparent and comprehensive protective barrier since it covers the entire body and is not restricted to any one area.[22] The thickness and characteristics of the skin alter in different parts of the body, but its basic function of protecting the body from chemicals, infections, and physical harm never changes.

Because the skin's primary job is to block the admission of foreign substances, it is a strong barrier for medication delivery. Nonetheless, scientists have devised many approaches to surmount this obstacle and improve medication administration through the dermis.[23] The following are a few of the main methods of transdermal medication delivery:

Stratum corneum penetration

The main barrier to drug penetration is the stratum corneum, the skin's outermost layer. Drug formulations are made to interact with or disturb this layer to get past this obstacle. Certain medications, for instance, are designed to have tiny, lipophilic molecules that may cross the stratum corneum, which is rich in lipids. Others may aid drug passage using chemical agents or penetration enhancers that momentarily damage the stratum corneum.

Reservoir systems

Reservoir systems for transdermal medication administration frequently have drug reservoirs that gradually release the drug over time. Usually, these reservoirs are integrated into skin-applied patches or devices. The medication is absorbed through the skin over time thanks to its slow release.

Iontophoresis

In this technique, charged drug molecules are driven through the skin using a small electrical current. It is possible to improve the transdermal administration of some medications, particularly ionic ones, using iontophoresis.

Microneedles

These small, painless needles penetrate the stratum corneum to form microchannels. Drugs can more easily flow through the skin thanks to these channels. Transdermal medication delivery is becoming more and more dependent on microneedle patches.

Nanoparticles and liposomes

Drug molecules can be contained in liposomes or nanoparticles, which are tiny vesicles that carry medications through the skin. These carriers can increase the penetration and stability of drugs.

Chemical enhancers

By momentarily rupturing the stratum corneum[24] and raising drug permeability, some substances, such as fatty acids and surfactants, can be utilized to improve drug penetration.

Transdermal patches

Adhesive patches with medication reservoirs are called transdermal patches. When they are administered topically, the medication is absorbed and released through the skin gradually over time.

Hydrogels

Medications can be carried in hydrogels, which are formulations[25] based on water that let the medications pass through the skin more easily. They have the ability to keep the skin moist, which improves the absorption of medications.

Here are some examples of drugs which can pass through skin barriers:

1. Nicotine (Stimulant)
2. Fentanyl (Synthetic Opioid)
3. Testosterone (Androgenic Hormone)
4. Clonidine (Antihypertensive)
5. Lidocaine (Local Anesthetic)
6. Scopolamine (Anticholinergic)
7. Methylphenidate (CNS Stimulant)
8. Rivastigmine (Cholinesterase Inhibitor)
9. Nitroglycerine (Vasodilator)
10. Estradiol (Steroid).

These all are used as a Transdermal Patch or Gel form.

EXCRETORY BARRIERS

In the context of drug delivery, an excretory barrier refers to the body's natural systems for removing substances, including medications, from the bloodstream and, ultimately, from the body. These systems operate as barriers, reducing the efficacy and duration of action of medications used for therapeutic purposes. The kidneys, liver, and other organs that filter,[26] metabolize, and excrete medicines are among the principal excretory barriers. Understanding and overcoming these obstacles is critical in medication development and delivery to guarantee that pharmaceuticals reach their target

tissues and exhibit the correct effects for the required period. To enhance treatment efficacy and reduce adverse effects, researchers and pharmaceutical corporations frequently devise drug formulations and delivery methods that can circumvent or modify these excretory barriers.

The organs and systems responsible for removing waste products, including medicines and their metabolites, are principally linked with excretory barriers in the human body. The following are the primary sites of excretory barriers in the human body:

Salivary glands

Because certain pharmaceuticals are expelled in saliva, which might be eaten or spat out, the salivary glands can help with drug excretion.

Kidneys

The kidneys are the principal excretory organs in the body, filtering the blood, eliminating waste products, and regulating the electrolyte and fluid balance. They are crucial in the removal of numerous medications and their metabolites through urine.

Skin

Although not a main excretory route, certain topical or transdermal drugs can be eliminated through the skin. Some medications can be absorbed through the skin and removed through perspiration or sebaceous glands.

Liver

The liver is an important organ in drug metabolism and excretion. It breaks down medicines and turns them into metabolites that are easier for the kidneys to excrete or remove through the bile into the GI system. The liver's function in drug metabolism can either help to eliminate medicines or transform them into active or dangerous versions.

GI tract

The GI system can serve as an excretory barrier for medications that are removed through feces. Some medications are excreted into the bile and subsequently into the small intestine. The medications can then be reabsorbed or excreted in the feces.

Lungs

The lungs may remove some volatile and gaseous medicines or their metabolites by exhale. This is especially true for anesthetics and gases used in medical procedures that are breathed.

These excretory barriers are critical in defining the pharmacokinetics of many medications (how drugs are absorbed, transported, metabolized, and removed). Understanding these pathways is critical for medication development and administration to improve therapeutic benefits while minimizing side effects or toxicities.

Following are the drugs which can cross through excretory barrier:
Many medications are made to pass excretory barriers to accomplish their therapeutic effects or to be removed from the body. Some examples of frequently used medications that can pass excretory barriers are:

Diuretics

Such as furosemide and hydrochlorothiazide, are medications that pass the renal barrier to enhance urine output, therefore removing excess salt and water from the body.

Antibiotics

Antibiotics such as penicillin, ciprofloxacin, and amoxicillin can overcome excretory barriers and reach infection sites to combat germs.

Chemotherapy medicines

Many chemotherapy medicines, such as doxorubicin and cisplatin, are designed to penetrate excretory barriers and reach and eliminate cancer cells throughout the body.

Antiviral medications

Such as tenofovir and acyclovir, are designed to target viral infections by passing through numerous excretory barriers, including the kidneys.

Antidepressants and psychotropic drugs

Medications such as fluoxetine (Prozac), sertraline (Zoloft), and lithium can overcome excretory barriers and enter the CNS, where they can influence mood and behavior.

IMMUNE SYSTEM

The immune system plays a significant role in drug delivery, often acting as both a protective barrier and a potential hurdle. As soon as a drug enters the body, it triggers the immune response. This response may vary according to the properties

of the medicinal product, including composition and origin. It is possible that the immune system recognizes the drug as a foreign substance or an antigen, leading to several consequences. One of the main mechanisms by which the immune system acts as a barrier[27] is to neutralize or remove the drug. This may have a significant impact on the efficacy and duration of action of the drug, as it can be rapidly removed from the bloodstream. In addition, a strong immune response may lead to adverse reactions or side effects. On the other hand, the immune system can also be harnessed for drug delivery purposes. Some drug delivery systems are designed to exploit the body's immune response to target specific cells or tissues. For example, immunoliposomes (nanoparticles coated with antibodies) can deliver drugs directly to cells with specific receptors, exploiting the natural affinity of the immune system to antigens.

In conclusion, the immune system plays a double-edged role in the delivery of drugs. It can hinder drug efficacy by trying to eliminate foreign substances, but it can also be manipulated to enhance drug targeting and delivery to specific sites[28] within the body. To develop safe and effective therapeutic treatments, it is important to understand the interaction between the immune system and drug delivery.

The concept of drugs "passing through" the immune system barrier is somewhat complex, as the immune system can influence drug clearance and, in some cases, enhance drug delivery. Nevertheless, certain drugs and drug delivery systems are designed to interact with the immune system. Here are some examples:

Vaccines

Vaccines contain antigens or weakened pathogens that stimulate the immune system to produce an immune response. They are used to prevent infectious diseases.

Immune checkpoint inhibitors

These drugs, such as pembrolizumab and nivolumab, block certain immune checkpoint proteins to enhance the immune response against cancer cells.

Nanoparticles for drug delivery

Nanoparticles can interact with the immune system to facilitate drug delivery to specific cells or tissues.

Liposomal drug delivery systems

Liposomes are lipid-based nanoparticles that can be used to encapsulate drugs and enhance drug delivery. Some liposomal formulations have been designed to interact with immune cells for targeted drug release.

Immunomodulators

Drugs such as interferons and interleukins are used to regulate the immune response and can be used in conditions such as multiple sclerosis or cancer.

Gene therapies

Some gene therapies use viral vectors that interact with the immune system to deliver therapeutic genes to target cells.

It should be noted that these drugs and delivery systems often work in concert with the immune system rather than "passing through" it in the traditional sense. It is designed to exploit or influence immune responses for therapeutic benefits, whether it promotes or inhibits specific immune reactions.

PLACENTAL BARRIER

Throughout pregnancy, a magnificent physiological structure known as the placental barrier –also called the placental membrane or the placental barrier – separates the circulatory systems of the fetus and the mother. This barrier is formed by the placenta, which develops in the uterine wall and serves as a necessary conduit for the exchange of food and gases between the child and the mother.

The placental barrier serves as a crucial protective barrier for drug delivery during pregnancy. It is a selective membrane that separates maternal and fetal circulatory systems to protect the developing fetus from potential harm while allowing the exchange[29] of essential nutrients and oxygen. However, this barrier may also be a significant obstacle for drug delivery.

Drugs given to pregnant women may pass into the maternal bloodstream and cross the placental barrier, potentially reaching the developing fetus. This is a challenge for drug delivery because the effects of the drug on the fetus[30] can be unpredictable and, in some cases, harmful. The permeability of the placental barrier to various drugs depends on factors such as the chemical properties, size, and charge. Some drugs can easily pass through the placenta, while others may be blocked. When prescribing or administering medications during pregnancy, pharmaceutical researchers and healthcare providers must consider the potential impact of the drug on the developing fetus. They must take into account the benefits of the treatment of maternal health conditions and the potential risks to the fetus. To know the safety of both the pregnant person and the unborn child, it is essential to understand how the placental barrier acts as a barrier in drug delivery.

The placental barrier is a remarkable anatomical and physiological structure located within the human body during pregnancy, specifically in the uterus. The placenta, which develops and attaches to the uterine wall, forms a unique

organ. This specialized barrier serves as a crucial interface between the maternal and fetal circulatory systems and plays a crucial role in pregnancy. The placental barrier has a number of vital functions, in particular as a protective shield and allowing a selective exchange of substances between the maternal and fetal bloodstreams. It provides essential nutrients, oxygen, and removes waste products from the developing fetus while protecting it from potential threats to the maternal bloodstream. This complex network of maternal and fetal tissues and blood vessels is essential to maintain a suitable and stable environment for fetal growth and development, making it a cornerstone of pregnancy biology.

Following are the categories of drugs which can pass through placental barrier:

1. Antibiotics
2. Analgesics
3. Antidepressants
4. Anticonvulsants
5. Antiretroviral medications
6. Antipsychotic drugs
7. Some maternal vaccination.

CONCLUSION

The complexity of biological barriers in drug delivery is a challenge and an opportunity in the field of pharmaceutical science. These barriers, such as the BBB, the GI barrier, the placenta barrier, and the immune system, play a crucial role in maintaining the health of the body and protecting it from harm. However, there are also restrictions on the efficient and targeted delivery of drugs. The research and development of drug delivery technologies continue to evolve with a view to overcoming these biological barriers. Innovative approaches, such as nanotechnology, liposomal drug delivery, and immunotherapies, make it possible to achieve more effective and precise drug treatments. An understanding of drug pharmacokinetics and pharmacodynamics, along with advancements in drug formulation and delivery systems, is shaping the future of medicine. The potential for safer and more effective drug therapies is growing as we continue to discover the details of these biological barriers. By exploiting our knowledge of these obstacles and exploiting the latest advances in drug delivery science, we have the opportunity to develop treatments that are not only more potent but also more targeted and patient-specific, thereby improving the quality of life for those in need of medical intervention. The ongoing effort to overcome these obstacles promises to revolutionize healthcare and provide new hope for patients facing a wide range of health challenges.

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Source of Support: Nil. **Conflicts of Interest:** None declared.