

Drug Delivery Strategies for Overcoming Biological Barriers

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Abstract

The therapeutic success of a drug depends not only on its pharmacological activity but also on its ability to reach the intended site of action in an adequate concentration. Following administration, therapeutic molecules must navigate a complex biological environment that includes cellular membranes, epithelial tissues, metabolic systems and specialised biological barriers. Although these barriers are essential for protecting tissues and maintaining physiological homeostasis, their selective nature can restrict drug absorption, distribution and access to protected organs and target tissues. The blood-brain barrier, blood-retinal barrier, placental barrier, skin, gastrointestinal barrier and blood-testis barrier are important examples that illustrate the challenges encountered during drug delivery. Drug properties such as molecular size, solubility, ionisation, protein binding and interactions with transport systems further influence barrier penetration and pharmacokinetic behaviour. This article discusses the major biological barriers encountered during drug delivery and examines strategies developed to navigate these obstacles. Approaches including drug modification, formulation optimisation, nanocarrier-mediated delivery, targeted delivery, alternative routes of administration and physical methods such as microneedles are discussed. Liposomes, micelles, nanogels, nanoemulsions and polymeric and other advanced carrier systems offer opportunities to improve drug stability, bioavailability, tissue distribution and controlled release. However, challenges related to safety, carrier stability, manufacturing, drug loading and translation from experimental models to clinical applications remain. The future of drug delivery therefore lies not in simply disrupting biological barriers, but in developing intelligent, selective and responsive systems that can navigate these barriers while preserving their essential protective functions.

Keywords: Biological barriers, Drug delivery, Therapeutic molecules, Drug carriers, Nanocarriers.

1. Introduction

A medicine can be highly effective against a disease in principle, yet fail to produce the desired therapeutic effect if it cannot reach its target in sufficient concentration. After

administration, a drug does not travel directly to its site of action. Instead, it must navigate a complex biological environment involving membranes, blood vessels, epithelial tissues, metabolic systems, transport proteins and

cellular defence mechanisms. Together, these structures and processes form biological barriers that regulate what enters, leaves and moves between different compartments of the body.

Biological barriers are essential for maintaining physiological balance and protecting sensitive tissues from pathogens, toxins and other foreign substances. At the same time, however, the same protective mechanisms can restrict the delivery of therapeutic molecules. The blood-brain barrier, for example, protects the central nervous system from potentially harmful substances circulating in the blood, but its highly selective nature also makes it difficult for many medicines to reach the brain. Similarly, the skin protects the body from the external environment but limits the penetration of many compounds applied to its surface.

This creates one of the fundamental challenges of modern drug delivery: how can we deliver the right drug, in the right amount, to the right place, while preserving the protective functions of the body's natural barriers?

2. What Are Biological Barriers?

Biological barriers are specialised anatomical, cellular and biochemical systems that control the movement of substances between different compartments of the body. They are not simply physical walls. Rather, they function as dynamic interfaces that selectively allow some molecules to pass while restricting others.

At the cellular level, biological membranes are largely composed of a semipermeable phospholipid bilayer. The ability of a molecule to cross these membranes depends on several factors, including molecular size, lipophilicity, ionisation, concentration gradients and protein binding. In general, small, lipid-soluble and predominantly unionised molecules tend to cross lipid membranes more readily than large or highly hydrophilic molecules.

However, passive diffusion is only one route of movement. Drugs may also cross

biological barriers through carrier-mediated transport, active transport or specialised processes such as receptor-mediated endocytosis. At the same time, efflux transporters can actively remove drugs from certain tissues, further limiting their accumulation at the desired site.

Thus, the ability of a drug to cross a barrier is determined not by a single property but by the interaction between the drug and the biological environment.

2.1. Why Does the Body Need These Barriers?

At first glance, biological barriers may appear to be obstacles standing between a drug and its target, but they are fundamental to survival. They protect tissues from potentially harmful chemicals, microorganisms and xenobiotics while maintaining the internal environment required for normal cellular function. They also regulate the movement of nutrients, oxygen, hormones and other essential substances. Therefore, the objective of drug delivery should not simply be to destroy or bypass biological barriers, but to achieve controlled and therapeutically useful passage across them.

2.2. The Major Biological Barriers in Drug Delivery

The human body contains several specialised barriers, each adapted to the requirements of the tissue it protects.

2.2.1. The Blood-Brain Barrier: Protecting the Brain, Challenging the Drug

The blood-brain barrier (BBB) is one of the most selective biological barriers in the body. It separates circulating blood from the central nervous system and is primarily formed by brain microvascular endothelial cells joined by tight junctions. Pericytes, the basement membrane and astrocytic end-feet further contribute to its structure and function.

Small and sufficiently lipophilic molecules may cross through passive diffusion, whereas essential nutrients use specific transport systems. At the same time, efflux transporters such as P-glycoprotein (P-gp),

breast cancer resistance protein (BCRP) and multidrug resistance-associated proteins (MRPs) can actively remove certain drugs from the brain.

The BBB therefore represents a classic example of the double-edged nature of biological barriers: what protects the brain can also prevent potentially useful medicines from reaching it.

2.2.2. The Blood-Retinal Barrier: Protecting Vision

The blood-retinal barrier (BRB) maintains the specialised environment required for normal retinal function. It consists of two major components: the inner barrier, formed by retinal vascular endothelial cells, and the outer barrier, associated primarily with retinal pigment epithelial cells.

Like the BBB, the BRB carefully regulates the movement of nutrients, drugs and other substances. Transporters such as P-gp and BCRP can further restrict the entry of certain drugs into retinal tissue. Consequently, systemically administered medicines may have difficulty reaching the retina in therapeutically useful concentrations.

2.2.3. The Placental Barrier: A Selective Interface Between Mother and Foetus

The placenta provides a highly specialised interface between maternal and foetal circulation. It allows nutrients and oxygen to reach the developing foetus while facilitating the removal of waste products. However, it is not an absolute barrier, and several drugs and environmental chemicals can cross it.

Drug transfer across the placenta is influenced by molecular size, lipid solubility, concentration, pH and protein binding. Transporters such as P-gp and BCRP may also influence foetal exposure by transporting certain substances back towards the maternal circulation.

2.2.4. The Skin: The Body's Protective Shield

The skin is the body's largest organ and its outermost defence against the environment.

Its structure, particularly the stratum corneum, creates a formidable barrier to the penetration of many chemicals and drugs.

For topical medicines, this barrier can be advantageous because it helps retain the drug within the skin. However, for transdermal delivery, excessive restriction of drug penetration can prevent sufficient quantities from reaching the systemic circulation. Drug properties, skin structure and formulation characteristics therefore play important roles in determining drug penetration.

2.2.5. The Blood-Testis Barrier

The blood-testis barrier limits the entry of numerous drugs into the testes and can therefore complicate the treatment of diseases affecting this protected compartment.

2.2.6. The Gastrointestinal Barrier

For orally administered medicines, the gastrointestinal tract represents one of the first major barriers encountered by a drug. The intestinal epithelium regulates the absorption of nutrients, water and medicines while limiting the entry of potentially harmful substances. Drugs may cross through intestinal cells via the transcellular route or between cells through the paracellular route. Transporters, metabolic enzymes and the gut microbiota can further influence drug absorption and availability.

3. What Determines Whether a Drug Can Cross a Barrier?

Not all drugs interact with biological barriers in the same way. The ability of a drug to cross a biological barrier is influenced by several physicochemical characteristics, including molecular size, lipophilicity, ionisation, polarity, aqueous solubility, plasma protein binding, chemical stability and affinity for transport proteins. In general, hydrophilic molecules may have difficulty crossing lipid-rich biological membranes by passive diffusion, whereas molecules with suitable membrane affinity may cross more readily. However, permeability is not determined by a single property; the combined influence of molecular size, charge, solubility, protein binding and interactions with transport systems



determines how effectively a drug reaches a particular tissue.

These considerations become even more important for macromolecular therapeutics such as peptides, proteins and nucleic acids, which often face additional challenges because of their large size and limited membrane permeability. The ability of a drug to navigate these barriers ultimately influences its pharmacokinetic journey through the body, encompassing absorption, distribution, metabolism and elimination (ADME). A drug may be poorly absorbed from the gastrointestinal tract, extensively metabolised before reaching systemic circulation, restricted from entering a particular tissue, or actively transported away from its intended site by efflux transporters.

Consequently, therapeutic efficacy depends not only on the intrinsic pharmacological activity of a drug but also on how efficiently it is absorbed, distributed and maintained at its target site. This interplay between drug properties, biological barriers and pharmacokinetics helps explain why a drug that demonstrates promising activity in an experimental system may behave very differently in the complex environment of a living organism.

4. Strategies for Drugs to Cross Biological Barriers

Strategies for crossing biological barriers are essential for improving drug delivery, enhancing therapeutic efficacy and achieving targeted drug distribution while minimising adverse effects. Biological barriers can restrict drug penetration, promote immune clearance of carriers and degrade therapeutic cargo before it reaches its intracellular target. These challenges often cannot be solved simply by increasing the drug dose; instead, successful delivery may require modifying the drug, optimising its formulation, choosing an appropriate administration route, or using a carrier that interacts favourably with its biological environment.

Modern delivery systems are therefore designed to protect drugs from degradation, improve their interaction with barriers and enhance accumulation at the site of action. By tuning properties such as size, morphology, surface chemistry, topography and environmental responsiveness, these systems can promote adhesion to and penetration through tissue, mucus and hydrogel barriers; transiently modulate barrier integrity; reduce immune recognition and clearance; and improve cellular uptake and intracellular trafficking. Dynamic, stimuli-responsive systems capable of sequentially interacting with different biological barriers thus offer an important route to more efficient and precise drug delivery.

4.1. Modifying the Drug

One approach to improving barrier crossing is to modify the drug itself. Chemical modification and prodrug strategies can be used to alter properties such as solubility, stability, membrane permeability and interactions with transport proteins. The purpose is not simply to make a drug more permeable, but to make its properties more compatible with the biological environment through which it must travel. Once the drug reaches the desired site, a prodrug may be converted into its active form. This approach can be particularly useful when the physicochemical properties of the original molecule limit its absorption or tissue distribution. However, changing the structure of a drug may also affect its pharmacological activity, metabolism and safety, so the modification must be carefully designed.

4.2. Improving the Formulation

In many cases, the active drug does not need to be chemically modified. Instead, its formulation can be redesigned to improve dissolution, stability, absorption or distribution. Formulation-based approaches are particularly useful for drugs that are poorly soluble, unstable in biological fluids or rapidly degraded before reaching their target. For example, lipid-based systems, emulsions and polymeric formulations can provide a

protective environment around the drug and influence how it interacts with biological membranes. Nanoemulsions, which consist of dispersed immiscible liquids, have been investigated as vehicles for improving the delivery and bioavailability of poorly soluble drugs.

4.3. Using Drug Carriers to Navigate Biological Barriers

Drug carriers are microscopic or nanoscale systems designed to help therapeutic agents overcome obstacles in the body while improving solubility, stability, bioavailability, circulation time, controlled release, biodistribution and tissue targeting. Because they can interact with biological structures at cellular and subcellular levels, micro- and nanocarriers are especially promising for crossing biological barriers.

Major examples include lipid-based systems such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers and lipid nanoparticles; polymeric systems including nanoparticles, micelles and dendrimers; inorganic and hybrid systems such as mesoporous materials, metallic nanoparticles and hybrid nanocarriers; and biological systems including extracellular vesicles and cell-derived platforms.

As these carriers must navigate multiple biological barriers, advanced systems are increasingly designed to interact with them sequentially—for example, by penetrating mucus, modulating tight-junction integrity, evading immune clearance and minimising immunogenicity to transport therapeutic cargo efficiently to its target site.

Incorporating a drug into a tailored carrier can improve its protection, transport and release. Liposomes can carry both hydrophilic and hydrophobic drugs, protect them from degradation and promote site-specific release. Micelles are useful for poorly water-soluble drugs because of their hydrophobic core and hydrophilic surface. Nanogels, which swell in aqueous environments, have been explored for transdermal and targeted delivery.

Carriers can also be adapted to challenging biological environments. Chitosan-based nanoparticles show mucoadhesive properties that may enhance mucus interaction and drug uptake in nasal or pulmonary delivery, while alginate-based systems have been investigated for mucosal delivery owing to their swelling and mucoadhesive behaviour.

4.4. Nanocarrier-Mediated Delivery

Nanocarriers are important because their very small size and modifiable surfaces help them interact with the body's barriers in ways that conventional medicines often cannot. Scientists can modify their surfaces to control how long they remain in the blood, how well they move through tissues, how easily they enter cells and how they travel inside cells. They can also protect medicines from breaking down too early and release them slowly or at the appropriate time.

Examples include nanogels, polymeric micelles, metallic nanoparticles, liposomes and other vesicle-like systems. Metallic nanoparticles have been studied for delivery through mucous membranes and the skin, while nanogels have shown promise for carrying drugs across the skin.

An important emerging direction is the design of responsive and nature-inspired carriers. Instead of reacting to only one barrier in the same way, these carriers can be designed to respond sequentially to different conditions in the body—for example, first interacting with mucus, then passing through tissue barriers and finally helping the drug enter cells.

4.5. Targeted Drug Delivery

Overcoming a biological barrier is only one step in successful drug delivery. After crossing the barrier, the drug must still reach the correct cells or tissue while avoiding unnecessary exposure to other parts of the body. Targeted drug delivery therefore aims to guide medicines to a specific biological site.

This can be achieved by modifying the surface of a carrier with molecules that recognise particular cell receptors or biological

structures, such as antibodies, peptides, ligands or cell-penetrating molecules.

These modifications help the carrier interact with selected cells and enter them through receptor-mediated processes. In this way, rather than physically breaking through the barrier, the delivery system attempts to use the barrier's own transport machinery.

4.6. Alternative Routes of Administration

When a biological barrier is particularly restrictive, changing the route of administration may provide a more practical solution. Alternative routes can reduce exposure to barriers encountered after conventional oral or systemic administration and may allow the drug to be delivered closer to its intended site. Important examples include:

- Intranasal delivery: Can provide access through the nasal mucosa and has been explored for delivering drugs that are difficult to transport through systemic routes.
- Transdermal delivery: Aims to bypass gastrointestinal absorption and first-pass metabolism, although the stratum corneum remains a major obstacle.
- Pulmonary delivery: Allows drugs to be administered directly to the respiratory tract but must overcome mucus and alveolar barriers.
- Ocular delivery: Can provide more direct access to ocular tissues and may reduce systemic exposure.
- Local administration: Delivering a drug directly into or near the target tissue can reduce the distance and number of barriers that the drug must cross.

4.7. Physical Approaches to Barrier Crossing

Physical methods can temporarily or locally alter the properties of a biological barrier to facilitate drug entry. These approaches are particularly useful when conventional formulations are unable to achieve sufficient penetration.

Microneedles are one example. They create microscopic pathways through the skin,

allowing substances such as vaccines, insulin, DNA, oligonucleotides and other therapeutic molecules to be delivered without relying entirely on passive diffusion through the stratum corneum.

Microneedle-based approaches have also been investigated for ocular delivery across the sclera or cornea.

Other physical approaches include ultrasound and electroporation, which can transiently modify tissue or cellular permeability and facilitate drug transport. The advantage of such approaches is that barrier modification can potentially be localised rather than affecting the entire body.

4.8. Barrier-Specific Delivery Strategies

No single delivery strategy can overcome every biological barrier. The choice of approach depends on the structure of the barrier, the properties of the drug and the location of the therapeutic target.

Biological barrier	Major delivery challenge	Potential strategies
Blood-brain barrier	Tight junctions and active efflux transporters	Receptor-mediated transport, targeted nanocarriers, intranasal delivery
Blood-retinal barrier	Restricted penetration into retinal tissues	Local ocular delivery, targeted carriers
Skin	Highly restrictive stratum corneum	Microneedles, lipid-based systems, permeation-enhancing formulations, transferosomes
Gastrointestinal barrier	Limited permeability, enzymatic degradation	Protective carriers, mucoadhesive systems,

	and first-pass metabolism	formulation optimisation, alternative routes
Placental barrier	Selective maternal–foetal drug transfer	Controlled or targeted delivery and careful exposure assessment
Blood-testis barrier	Restricted penetration into testicular tissue	Targeted or local delivery approaches
Nasal barrier	Mucociliary clearance and epithelial restriction	Mucoadhesive carriers, chitosan-based systems, intranasal formulations
Tumour vasculature	Poor blood flow, heterogeneous vasculature permeability and high interstitial pressure	Targeted nanocarriers, active transport strategies, and high vascular-targeting approaches

The examples above illustrate an important principle: the strategy must be matched to the barrier. A carrier that performs well in the gastrointestinal tract may not be suitable for the brain, while a system designed for transdermal delivery may not be appropriate for a protected internal organ. The biological environment therefore needs to be considered during the design of both the drug and its delivery system.

4.9. From Passive Delivery to Intelligent Drug Delivery

An important direction in modern drug delivery is the shift from simple passive transport towards systems capable of active, sequential and responsive interactions with biological barriers. Passive transport generally depends on concentration gradients, whereas

active transport can use cellular energy to move selected molecules across a barrier.

This concept is particularly relevant to complex targets such as solid tumours, where inadequate blood flow, heterogeneous vasculature, hypoxia and elevated interstitial pressure can all restrict drug delivery. Strategies that actively interact with tumour vasculature or use specific transport mechanisms are therefore being investigated to improve drug accumulation within tumours.

Ultimately, the goal of overcoming biological barriers is not to eliminate these barriers, since they perform essential protective functions. The objective is to develop delivery systems that can selectively navigate, bypass or temporarily interact with a barrier while preserving normal tissue protection. This is why modern drug delivery increasingly combines knowledge of pharmacology, materials science, biology and physiology to design systems that can carry a drug from its site of administration to the cells where it is actually needed.

Conclusion

Biological barriers are essential for maintaining tissue integrity and protecting the body from harmful substances, yet their highly selective nature remains one of the major obstacles to effective drug delivery. From the blood-brain barrier and blood-retinal barrier to the skin, gastrointestinal tract and placental interface, each barrier presents distinct physical, cellular and biochemical challenges that can limit the absorption, distribution and accumulation of therapeutic agents. Consequently, successful drug delivery depends not only on the pharmacological properties of a drug but also on the ability of the delivery system to navigate the biological environment between the site of administration and the intended target.

Recent advances in drug modification, formulation science, nanotechnology, targeted delivery and alternative routes of administration have created new possibilities for overcoming these challenges. Nanocarriers

such as liposomes, micelles, nanogels, nanoemulsions and polymeric systems can protect therapeutic molecules from premature degradation, improve their solubility and stability, and influence their distribution within the body. Targeted and responsive delivery systems further offer the possibility of directing drugs towards specific tissues or cells while reducing unnecessary exposure to healthy tissues. These approaches demonstrate that overcoming a biological barrier does not necessarily require its complete disruption; rather, successful delivery can be achieved by exploiting, bypassing or selectively interacting with the mechanisms that regulate transport across the barrier.

Despite these advances, translating sophisticated delivery systems from experimental studies into reliable clinical applications remains challenging. Differences in barrier properties between experimental models and humans, variability in drug loading and release, carrier stability, manufacturing complexity and concerns regarding toxicity all need to be carefully considered. Future progress will therefore depend on the development of more predictive preclinical models, a deeper understanding of barrier biology and the rational engineering of safer and more efficient delivery systems. Particular attention will also be required to achieve an appropriate balance between therapeutic efficacy and safety.

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