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# Current common prodrug delivery methods and biochemical property

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**Abstract.** Prodrugs are pivotal in overcoming drug delivery and absorption challenges. These bioreversible derivatives are strategically designed to address medicines' poor bioavailability and administration constraints. Prodrugs offer versatile solutions for various delivery methods, including oral, dermal, nasal, and central nervous system (CNS) routes and tumor targeting. This literature review aims to summarize several prodrugs delivery methods. The report also focuses on the common concepts of prodrug design. The utilization of prodrugs also includes innovative strategies, such as receptor-mediated internalization and responsive drug release, demonstrating promising outcomes for cancer therapy. The application of prodrug methods is comprehensive. Prodrugs emerged as a universal approach to improve drug administration and absorption, with their applications spanning diverse medical contexts. By tailoring prodrugs to specific delivery routes and addressing unique challenges, researchers open avenues for more effective and targeted therapies. Further exploration and optimization of prodrug strategies hold the potential to revolutionize drug delivery in clinical settings. Although prodrugs have many advantages, there are still many possible future improvements. Many diseases or target organs still need help applying prodrugs even though the current drug design needs this technology for administration. Future research should focus on the lack of chemical stability, including considering the balance between aqueous solubility and lipophilicity. Also, the elimination of the formation of degradation by-products or the design of acceptable metabolism pathways is another aspect that should be considered.

**Keywords:** Prodrug, drug delivery, lipophilicity, aqueous solubility

## 1. Introduction

Prodrugs are bioreversible derivatives of drugs that are usually specifically designed to address challenges related to drug delivery and absorption in the body. When developing a new drug to treat a particular symptom or disease, scientists must consider various factors, including the drug's biochemical properties and the site of absorption in the body. For example, some drugs may have excellent therapeutic efficacy but poor bioavailability due to limited absorption in the gastrointestinal tract. Additionally, some medications may only be effective when administered via injection, which can be challenging for patients with acute phobia or those requiring long-term treatment. Prodrugs are designed to overcome these issues by undergoing chemical or enzymatic transformation in the body, Releasing the active parent drug that can exert the desired pharmacological effect [1, 2]. The structural and biochemical properties of the prodrug, as well as its conversion to the active parent drug, are closely

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linked to the delivery method used. This article discusses various prodrug delivery methods and provides examples of how prodrugs designed using each method can achieve optimal absorption for improved therapeutic outcomes. Prodrugs offer a promising approach to enhancing drug delivery and bioavailability, addressing drug absorption and administration challenges.

## 2. Several delivery approaches

### *2.1. Oral prodrug*

The administration of oral prodrug is often achieved by taking the pill or electuary, and the main biosorption to the metabolic pathway happens at the stomach and intestine. The oral bioavailability of a candidate drug is mainly related to aqueous solubility and permeability.

*2.1.1. Improved aqueous solubility.* Most drugs have the problem of poor aqueous solubility [3]. The poor water solubility may imply many factors related to oral bioavailability. First, the medicine with poor water solubility may need a larger dose to accomplish the sufficient concentration of the active drug. However, it is more challenging to deliver a larger quantity. Another reason is that poor water solubility often has high melting points and crystallinity [4]. The design of an oral prodrug is not the only approach to solving those problems. Still, it provides an alternative way when other standard physical and chemical solutions do not work well.

*2.1.2. Improved lipophilicity.* One of the most common strategies for improved lipophilicity is to design an ester prodrug. The original polar, ionizable, hydrophilic functional groups are often replaced or masked, promoting the drug lipophilicity, membrane permeation, and oral absorption increases. Oseltamivir is a good example here. It is the ethyl ester prodrug of the antiviral molecule oseltamivir carboxylate. Oseltamivir carboxylate is an influenza A and B neuraminidase (NA) (sialidase) inhibitor. The active parent drug is the ester hydrolysis form of Oseltamivir. The main difference that Oseltamivir has to achieve higher oral absorption is that the hydroxyl group of the active drug, which is polar, is replaced by methyl, which is less polar. The overall lipophilicity of the prodrug increases, which promotes prodrug membrane accessibility. In the human body, Oseltamivir can be orally uptake via pills and get into metabolism. Human carboxylesterase 1 (CES1)is the natural enzyme in the normal human body. The main enzyme responds to Oseltamivir and undergoes bioconversion to Oseltamivir carboxylate. Although this process will result in the production of ethanol, it is just small quantities of by-products [5]. However, active drugs' absorption and bioconversion rates become much faster—the oral bioavailability increases from 5% to 79% [1].

### *2.2. Dermal drug delivery*

Compared to the oral prodrug, which is internal, dermal prodrug delivery is topical and mainly depends on skin absorption. However, the strategy of improving drug absorbability related to drug permeation for dermal prodrug is similar to the oral prodrug. Since the lipid exits in various forms and layers of skin, it is common to think that lipid solubilities help the dermal prodrug's permeation more. High lipophilicities and poor aqueous solubility could result in poor overall dermal absorbability [6, 7]. Like oral prodrug, water and lipid solubilities, in addition to the balance of those two factors, should be considered during the designation of dermal prodrug.

One example of a parent drug with a designed dermal prodrug is naproxen. It is widely used to treat rheumatic diseases. As a potent nonsteroidal anti-inflammatory drug, naproxen contains the ionizable carboxylic acid group that is highly hydrophilic. This property may be the leading cause of the low bioavailability of topical administration: only 1–2%. However, scientists have designed piperazinyl alkyl prodrugs to solve this problem. The modified piperazinyl alkyl functional group provides high aqueous solubility and lipophilicity to the molecule. Within those properties that are different from the parent drug, the bioabsorbility significantly increases.

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One example to demonstrate the importance of balancing aqueous solubility and lipophilicity in dermal prodrug is 5-iodo-2′-deoxyuridine. Too high lipophilicity alone may not proportionally increase permeability in dermal administration. 5-iodo-2′-deoxyuridine (IDU), although an effective treatment of skin herpes simplex keratitis, has poor skin permeability due to its high polarity. Five different oligoethylene ester derivatives (9-13) were tested. The larger numerical order means the longer polyoxyethylene chain length, which is also responsible for improving lipophilicity. However, with the addition of polyoxyethylene, only the first two ester derivatives(9 and 10) show better permeability than the parent drug. All other 3, reversely, have less skin permeability due to the poor aqueous solubility caused by high lipophilicity [9].

### *2.3. Nasal*

While oral prodrugs rely on systemic administration and dermal prodrugs mainly depend on topical administration, nasal prodrugs have more alternatives. They could be either systemic or topical. Nasal systemic drugs depend on many factors, including the drug's physical state, morphology, solubility, and other chemical states. A prodrug is one solution that improves absorption based on changing chemical properties [9]The nasal mucosa is present as an absorption barrier in nasal prodrug delivery. The mucosa is not just a physical barrier but also an immunological and enzymology barrier. The nasal membrane consists of a lipoidal and aqueous pore pathway, and nasal prodrugs need to be administered transnasally to pass through the epithelial cell layers to reach the systemic circulation. Drug passage through the barrier can occur through the transcellular or paracellular route. As part of the immune system, nasal mucociliary clearance is a protective mechanism that draws particles toward the nasopharynx, constituting a temporal barrier to transnasal absorption. Various enzymes exist in substantial quantities in the nasal epithelia, including aldehyde dehydrogenase, glutathione transferase, and carboxylesterases, which can cause the pre-systemic degradation of peptides and proteins. The common prodrug concept is used to solve those problems, increasing absorption [10]. The most commonly used ester prodrug strategy still works here.

In addition, due to its physical location in the human body, nasal prodrugs are often applied in noninvasive brain target therapy [11]. Intranasal administration is relatively close to the drug's destination and drain. A prodrug with nasal delivery may not need as much consideration of stability as a prodrug from other delivery since it will usually not travel so long in the metabolism pass way, including the liver. Also, toxicity is another element to pay more attention to without passage through the liver.

The paragraph above mentioned the prodrug's utilization for brain targets, which means the broadly applied principle could be specified for the situation. Other than the classification of administration, prodrug delivery could also be classified by satisfying various target organs other than the brain.

### *2.4. Central nervous system (CNS) drug delivery*

The central nervous system (CNS) is one of the most important places of signal and communication in our body. Since CNS chemical and electrical signals that CNS uses are susceptible to the microenvironment, our body needs particular barriers to prevent unwanted disruption. The blood–brain barrier (BBB) is one of them. It is a very condensed tissue wall combined with endothelial cells and capillaries. There are only several types of ion channels, and transporters allow the optimal potential of signal transmission [12]. As a result, BBB almost let no large or small molecule get through. This area remains not fully understood, and current research has shown its importance in preventing viruses and bacteria so that we could not remove it for drug administration [13]. Indeed, BBB is the primary rate-determining barrier of CNS drug delivery [14]. To cross BBB, one possible solution is, again, to increase lipophilicity. However, high lipophilicity solely may not always work.

Many different factors work together. These factors include the permeability of the blood-brain barrier, the concentration in plasma over time, and local cerebral blood flow. The balance between lipophilicity and hydrophilicity is crucial for transport within and across the blood-brain barrier. Adding lipophilic groups to a compound alters its partition coefficient and enhances its ability to penetrate the

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blood-brain barrier. However, some drugs, such as chlorambucil, face limitations in brain entry due to their polar nature. Binding to plasma proteins is essential for drug stability, but it can also restrict the delivery to target tissues. Esterification of drugs can modify their properties, such as lipophilicity and binding capacity to plasma proteins. Their chain length and shape influence the hydrolysis of esters in plasma. Chlorambucil esters undergo rapid hydrolysis, releasing chlorambucil, but their brain penetration is limited. When chlorambucil esters are administered, lower concentrations of active compounds are observed in plasma and brain compared to equimolar chlorambucil administration. Rapid hydrolysis of esters leads to the release of chlorambucil, and its presence in an ionic form reduces its concentration in the brain. These findings suggest that the examined lipophilic chlorambucil esters are unsuitable for human brain tumor treatment, but studying them can provide insights for developing better drug formulations with improved brain penetration [15].

### *2.5. Tumor targeting.*

Most tumor comes from unlimited mutated cell growth. The mutated cell cluster together and sometimes even form extra blood vessels to satisfy the nutrition delivery. Tumor, in short, forms from the cells of patients themselves. This is the main challenge of drug administration and effect. It is hard for drugs to distinguish tumor cells from normal cells. One solution is to make the drug target the fast-proliferated cell. However, some normal body cells, like our hair, have the same feature. The present study investigates the potential of hyaluronic acid (HA) prodrugs as a novel strategy for tumor targeting in the treatment of prostate cancer. Specifically, the researchers developed a boronated HA derivative known as HABQ, an example of a tumor-targeting prodrug.

Tumor targeting is crucial for effective cancer therapy, as it allows for the selective delivery of therapeutic agents to the tumor site, minimizing off-target effects and enhancing therapeutic efficacy. In this regard, the enhanced permeability and retention (EPR) effect has emerged as a critical mechanism to exploit for tumor targeting. The EPR effect takes advantage of the leaky and disorganized vasculature in solid tumors, allowing macromolecules like HABQ to accumulate preferentially in tumor tissues. Consequently, HABQ demonstrated significant accumulation in solid tumors, laying the foundation for its tumor-targeting potential.

Moreover, the unique structure of HABQ played a pivotal role in facilitating tumor targeting. By disrupting intramolecular hydrogen bonds between carboxylates and acetamides, HABQ achieved a less rigid chain, enhancing its flexibility and interactions with target receptors on tumor cells. The study revealed that HABQ exhibited a receptor-mediated internalization mechanism through interactions with CD44 receptors on an inflamed vascular endothelium. This specific internalization mechanism enabled efficient binding and uptake of HABQ by tumor cells, further supporting its tumor-targeting capabilities.

The prodrug HABQ also demonstrated responsive drug release characteristics, releasing quercetin primarily under acidic conditions, such as those encountered in the tumor microenvironment. This localized release of quercetin within the tumor site led to dose-dependent anti-inflammatory effects, providing additional benefits to its tumor-targeting efficacy.

Overall, HABQ represents a promising example of a tumor-targeting prodrug with favorable properties for cancer therapy. Its ability to leverage the EPR effect, receptor-mediated internalization, and localized drug release highlights its potential as a targeted therapeutic approach for prostate cancer and potentially other solid tumors. While the study provides compelling evidence for the tumor-targeting potential of HABQ, further investigations are warranted to fully elucidate the intricate interactions and optimize the therapeutic benefits of HA prodrugs for clinical applications in cancer treatment [16].

## 3. Conclusion

Prodrugs, as bioreversible derivatives of therapeutic agents, offer an innovative and versatile solution to the challenges associated with drug delivery and absorption. Their strategic design addresses poor bioavailability, limited absorption, and administration constraints. Prodrugs showcase their potential as a universal approach to enhance drug administration and absorption, spanning a broad spectrum of medical fields. By tailoring prodrugs to specific delivery routes and addressing unique challenges,

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researchers pave the way for more effective and targeted therapies. However, despite their numerous advantages, challenges remain to overcome, such as chemical stability and elimination of degradation by-products. Future research should optimize these aspects to further harness prodrugs' transformative potential, ultimately reshaping drug delivery paradigms and advancing clinical treatments. Current prodrugs often face problems of balancing aquatic solubility and lipophilicity to optimize absorption. However, these two chemical features are relatively opposite to each other. Another challenge is optimizing the delivery passway. Although there are multiple delivery mechanisms of different prodrugs, there are still barriers to reaching the target, like BBB in CNS. More reachable target organ is also a consideration.

**References**

[1] Jarkko Rautio HK, Tycho Heimbach, Reza Oliyai, Dooman Oh, Tomi Järvinen and Jouko Savolainen. Prodrugs: design and clinical applications. 2008;7.
[2] Yanxiu Ge YM, Lingbing Li. The application of prodrug-based nano-drug delivery strategy in cancer combination therapy. 2016.
[3] Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. 2000.
[4] Valentino J. Stella KWN-A. Prodrug strategies to overcome poor water solubility. 2007.
[5] Fred Y Aoki KED. Oseltamivir: a clinical and pharmacological perspective. 2001.
[6] Antiviral prodrugs-the development of
[7] Jarkko Rautio * TN, Hannu Taipale , Jouko Vepsalainen , Jukka Gynther , a a Krista Laine , Tomi Jarvinen. Piperazinylalkyl prodrugs of naproxen improve in vitro skin permeation. 2000.
[8] FRANCESCO PAOLO BONINA MGR, LUCIA AVALLONE, FRANCESCO BARBATO, MARZIA AMATO, CARMELO PUGLIA, MAURIZIO RICCI, PAOLO DE CAPRARIIS. New Oligoethylene Ester Derivatives of 5-Iodo-20-deoxyuridine as Dermal Prodrugs: Synthesis, Physicochemical Properties, and Skin Permeation Studies. 2001.
[9] C.R. Behl HKP, A.P. Sileno, J. deMeireles, V.D. Romeo. Effects of physicochemical properties and other factors on systemic nasal drug delivery. 1997.
[10] Giridhar S Tirucherai CYAKM. Prodrugs in nasal drug delivery. 2001.
[11] Abdur Rauf Khan ML, Muhammad Wasim Khan, Guangxi Zhai. Progress in brain targeting drug delivery system by nasal route. 2017.
[12] N. Joan Abbott AAKP, Diana E.M. Dolman, Siti R. Yusof, David J. Begley. Structure and function of the blood–brain barrier. 2010.
[13] Pardridge WM. Why is the global CNS pharmaceutical market so under-penetrated? 2002.
[14] Jarkko Rautio KL, Mikko Gynther, Jouko Savolainen. Prodrug Approaches for CNS Delivery. 2008.
[15] Nigel H. Greig SG, Eileen M. Daly, Daniel J. Sweeney, and Stanley I. Rapoport. Physicochemical and pharmacokinetic parameters of seven lipophilic chlorambucil esters designed for brain penetration. 1990.
[16] Vincenzo Quagliariello AG, Som Akshay Jain, Francesco Rosso, Rosario Vincenzo Iaffaioli, Alfonso Barbarisi, Manlio Barbarisi, Nicola Tirelli. Double-responsive hyaluronic acid-based prodrugs for efficient tumour targeting. 2021.