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Ester-Based Prodrugs: Rational Design, Mechanistic Insights, and Translational Applications in Neurology and Dermatology

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Abstract. The blood-brain barrier and the skin's stratum corneum restrict the access to target tissues for central nervous system (CNS) and dermatological drugs; systemic administration frequently causes side effects in other parts of the body. Imbalance of cutaneous neuroimmune signals is related to itching in atopic dermatitis and to peripheral sensitization in postherpetic neuralgia, indicating the necessity of drug delivery methods that integrate barrier penetration with local activation at the desired site. Ester prodrugs link the parent drug to a carrier through a reversible ester bond and are activated by esterase hydrolysis; they are extensively applied because of their structural flexibility and controllable activation. The main idea of their structure is to regulate the steric hindrance and electrical properties of the ester bond in order to achieve a good balance between systemic stability and efficacy in the target tissue. The expression of esterases and substrate specificity can lead to different activations in different places. For CNS delivery, esterification might enhance the permeability of the blood-brain barrier, while amino acid groups can facilitate uptake by LAT1; the release is dependent on the specific bioconversion pathway of the prodrug. In the skin, the local esterase activity supports in situ hydrolysis, but the responsible enzymes and their effects are influenced by the type of substrate and the model. This paper systematically discusses the design principles of ester prodrugs, mainly focusing on their translational applications in the fields of neurology and dermatology. In summary, the clinical application will involve solving the problems of esterase variability, premature hydrolysis, and the safety of leaving groups by using predictive models and specific activation strategies in different tissues.

Keywords: ester prodrugs, blood–brain barrier, central nervous system, skin stratum corneum, skin–nerve axis

1. Introduction

Dermatological and neurological disorders remain difficult to treat because effective drugs must cross either the stratum corneum or the blood-brain barrier while avoiding excessive systemic toxicity.

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The skin and nervous system also interact through neuroimmune signaling, which is relevant to conditions such as pruritus and postherpetic neuralgia. Delivery strategies that combine barrier penetration with local activation therefore have particular translational value.

Ester prodrugs chemically mask polar groups on active drugs and are later hydrolyzed by esterases to release the parent compound. By tuning carrier structure, steric hindrance, and tissue-specific activation, this approach can improve permeability, pharmacokinetics, and local exposure.

This review summarizes rational design, enzymatic activation, and representative applications of ester prodrugs in neurological and dermatological drug delivery.

2. Principles of the rational design of ester prodrugs and their mechanisms of action

2.1. Fundamentals of chemical structure design for ester prodrugs

The chemical structure design of ester prodrugs begins with the identification of modifiable sites on the parent drug. The functional groups in the parent drug molecule that can be used to introduce ester bonds mainly fall into main categories: hydroxyl groups (alcohol or phenolic), which form carboxylates by reacting with carboxylic acids; carboxyl groups, which form corresponding alkyl esters by reacting with alcohols; and phosphate or phosphonate groups, which form phosphates by reacting with alcohols. Most recently, carbonates and amides, both structurally classified as "carbonyl-oxygen/nitrogen" linked esters, have also been systematically included in the design of ester prodrugs [1]. The selection of modification sites and carrier groups requires a comprehensive evaluation of the parent drug molecule's chemical environment, the intended pharmacological targets, and the enzymatic environment in vivo.

A well-designed ester prodrug should meet the following basic criteria, often referred to as the "golden rules" of its design: the prodrug itself should have no or very weak activity against any pharmacological targets; it should possess sufficient chemical stability within a specific pH range (typically meaning it remains intact during formulation storage and gastrointestinal transit); it possesses sufficient water solubility to meet formulation and dissolution requirements; it can be rapidly and quantitatively converted into the active parent drug in vivo; and the released carrier moiety should be non-toxic, preferably an endogenous metabolite or an inert molecule confirmed to be safe [2]. In particular, the selection of the carrier group is a key aspect of chemical structure design. The chemical structure of the carrier group, including its steric bulk, electronic effects, lipophilicity, and ability to leave the complex, directly influences the hydrolysis rate of the ester bond and the enzyme's recognition properties. Generally, esters with high steric hindrance (such as p-t-butyroxymethyl ester) hydrolyze more slowly, whereas esters such as p-nitrophenol esters hydrolyze more rapidly due to the strong leaving group ability of the phenoxy group. However, because the leaving groups released by these esters are potentially toxic, both types have gradually fallen out of favor in mainstream design [3]. The current trend in the design of modern ester prodrugs is to use carrier groups with simpler structures and safer metabolites or to predict and screen for optimized structures using computational biology methods. The overall design and evaluation workflow is summarized in Figure 1.

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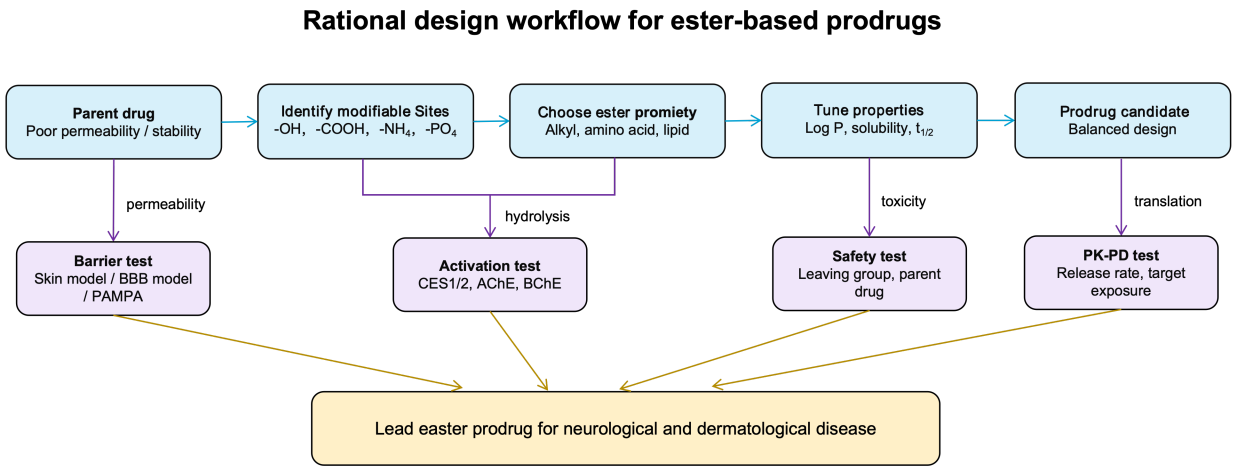


Figure 1. Rational design workflow for ester-based prodrugs

Note: This workflow iteratively optimizes ester prodrugs for improved permeability, controlled hydrolysis, and safety, yielding leads for neurological and dermatological diseases.

2.2. Esterase-mediated hydrolytic activation and tissue-targeted design

2.2.1. Chemical and enzymatic hydrolysis pathways

The biotransformation of ester prodrugs is primarily mediated by carboxylesterases (CES) from the serine hydrolase superfamily in vivo. Human CES are predominantly divided into two subtypes: hCE1 (CES1A1) and hCE2 (CES2A1), which differ substantially in tissue distribution, substrate specificity, and biological function[4-6]. Both subtypes share a Ser-His-Glu/Asp catalytic triad as their active site; the hydrolysis process proceeds through the canonical two-step "acylation-deacylation" mechanism: the active serine residue first initiates a nucleophilic attack on the carbonyl group of the ester bond, forming a tetrahedral intermediate; subsequently, the leaving group (an alcohol or phenol) is released, yielding an acyl-enzyme covalent intermediate; this intermediate is then hydrolyzed by a water molecule, releasing free carboxylic acid and restoring enzyme activity [7, 8]. With respect to substrate recognition, hCE1 and hCE2 follow basic structural patterns: hCE1 preferentially hydrolyzes ester substrates containing smaller alcohol groups (i.e., esters with smaller alcohol moieties and larger acyl moieties); typical substrates include oseltamivir and clobetasol. hCE2 preferentially hydrolyzes ester substrates containing smaller acyl groups (i.e., esters with smaller acyl moieties and larger alcohol moieties), with typical substrates including heroin and fluorescein diacetate [4]. In the nervous system, although CES expression levels are generally low, certain ester-containing diagnostic probes, such as acetylcholinesterase (AChE) substrate analogs used in positron emission tomography (PET) imaging, can be specifically hydrolyzed by AChE in the synaptic cleft; this principle has been applied to the in vivo imaging of AChE activity in Alzheimer's disease (AD) [9].

2.2.2. Tissue distribution of esterases and targeted activation

The tissue-specific distribution of esterases provides a molecular basis for "targeted activation" in tissue-specific applications. hCE1 is mainly expressed in hepatocytes and lung tissues, while hCE2 is mainly found in small intestinal epithelial cells and kidneys [10, 11]. Esterase activity has been observed in human skin and keratinocyte models, and the transcripts of CES1 and CES2 have been

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detected; however, the specific enzymes for different substrates and their regulation in inflammatory lesions are not clearly defined yet [12]. Therefore, the recognition of various tissue esterases can be distinguished by varying the size of the acyl and hydroxyl groups in the ester bonds: enlarging the steric bulk of the acyl group decreases the binding ability of hCE2, keeping the prodrug mainly in the intestine, where it is primarily converted into the active form by hCE1 in the liver after entering the systemic circulation. The construction of fexofenadine prodrugs follows this method to modify steric hindrance effectively, successfully establishing a metabolic pathway characterized by "intestinal stability and liver-specific conversion." This technique avoids the loss due to the hydrolysis in the first-pass metabolism, thus ensuring high oral absorption efficiency of the drug [13, 14]. In addition, arylacetamide deacetylase (AADAC) also participates in the metabolism of intestinal ester prodrugs; especially its substrates overlap with some CES2 substrates, which should be considered during the design process [15].

Due to the differences in tissue localization between the CES subtype and AADAC, many prodrugs have been found to be selectively activated in certain organs. Simvastatin and lovastatin are given as lactones and are transformed into the active hydroxy-acid form through esterases in the intestinal, hepatic, plasma, and other tissue compartments. The hydrolysis of the compounds differs among individuals; thus, these drugs cannot be considered as liver-specific CES1-activated prodrugs, and their activation will not prevent the occurrence of muscle side effects caused by statins [16]. The inhaled glucocorticoid ciclesonide itself has no pharmacological activity, but it is converted into a very potent metabolite under the action of pulmonary epithelial esterases, leading to a significant enhancement of local anti-inflammatory activity and a decrease in systemic exposure, thereby reducing the risk of steroid-related adverse effects [17, 18]. When applied to the skin, topical glucocorticoid prodrugs (such as hydrocortisone butyrate and mometasone furoate) are efficiently hydrolyzed by the epidermal CES2 enzyme into highly active alcohol forms during the passage through the stratum corneum. Since these active metabolites have a strong binding affinity with their receptors, they are "fixed" at the application site, greatly reducing the systemic absorption [19]. In the nervous system, except for the small amount of CES present in the endothelial cells of the brain's microvessels, prodrugs can also be designed based on the high expression of AChE near cholinergic synapses to achieve targeted drug release into the synaptic cleft, which can improve cognitive function [20]. Alternatively, ester prodrugs can be actively transported into the brain through the L-type amino acid transporter 1 (LAT1), which is highly expressed in the BBB, and then slowly activated by esterases in the brain parenchymal cells, thus keeping a prolonged drug concentration in the brain field [21].

3. Translational applications of ester prodrugs in neurology

The main obstacle for CNS delivery of ester prodrugs is the BBB; their design concept has changed from the passive "lipid-enhanced permeation" to a dual-track strategy that integrates active "transporter hijacking" and "enzyme-controlled activation." In the three major therapeutic domains —neurodegenerative, neuropsychiatric, and neuroprotective/regenerative—this method has achieved many clinical successes; however, some problems have been discovered, such as esterase selectivity, formulation stability, and clinical translation. This part will introduce the basic mechanisms of CNS delivery and the present status of applications in these fields.

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3.1. Increasing lipophilicity to promote passive diffusion

Esters function as prodrugs by covalently covering the ionizable groups in the drug molecules, thus increasing the Log P/D value and allowing amphipathic ions or highly polar compounds to pass through the lipid bilayer of the BBB by utilizing the concentration gradient. Once in the brain, they are hydrolyzed by enzymes such as CES1 and CES2, releasing the active parent drug. Baclofen is a gamma-aminobutyric acid (GABA) B receptor agonist; its amphiphilic nature results in extremely poor penetration of the BBB. A systematic comparison of the relationship between the physicochemical properties and BBB permeability of a series of baclofen prodrugs—ranging from methyl ester to butyl ester—revealed that the lipophilicity of the isopropyl ester (Log D = 1.27) was approximately 170 times higher than that of the parent drug (-0.96). This increase in lipophilicity also enhances P-gp affinity (IC_{50} decreased from 1,300 μM for the methyl ester to 290 μM for the isopropyl ester). Despite efflux, the concentration of the methyl ester in the brain remains significantly higher than that of the parent drug, indicating that the design of ester prodrugs must strike an optimal balance between passive diffusion and P-gp recognition in terms of chain length [22].

3.2. Neurodegenerative and neuroimmune diseases

3.2.1. Parkinson's disease (PD)

PD is a neurodegenerative disease characterized by the degenerative loss of dopaminergic neurons in the substantia nigra and motor dysfunction. Dopamine replacement therapy is the cornerstone of treatment for this disease. As a direct precursor of dopamine, L-DOPA faces pharmacokinetic (PK) challenges in patients with mid- to late-stage disease, characterized by unstable gastrointestinal absorption and delayed gastric emptying, which result in a slow onset of action. L-DOPA ethyl ester (LDEE) significantly improves the drug's gastric solubility and intestinal permeability through esterification of the carboxyl group, allowing for faster absorption and hydrolysis by nonspecific esterases into L-DOPA, thereby markedly shortening the time to peak concentration [23]. Clinical studies have confirmed that LDEE oral solution, as well as subcutaneous or intramuscular injections, can be used as a rapid-relief strategy for "off periods" in patients with Parkinson's disease, effectively overcoming the difficulties in symptom control caused by fluctuations in the absorption of oral L-DOPA [24, 25].

3.2.2. AD

AD is a neurodegenerative disease characterized by progressive cognitive decline and synaptic loss. Cholinergic dysfunction and limited drug delivery to the brain are key obstacles to its treatment. The prodrug NT-0796 (ruvonoflast), modified with an isopropyl ester, selectively inhibits neuroinflammation mediated by the NLRP3 inflammasome [26]. Once entering the brain, it is hydrolyzed by CES1—which is expressed locally in microglia—into the active carboxylic acid metabolite NDT-19795. In vitro studies have shown that NT-0796 exhibits high permeability in a BBB model using brain endothelial cells derived from human induced pluripotent stem cells; PK studies in non-human primates have confirmed that its activation in the brain primarily depends on CES1 in brain tissue, while cerebrospinal fluid itself lacks metabolic capacity. This candidate molecule has now entered Phase II clinical development [27].

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3.3. Neuropathic pain

Glutamate carboxypeptidase II (GCPII) inhibitors reduce the hydrolysis of N-acetylaspartylglutamate in the CNS, thereby indirectly regulating glutamatergic neurotransmission. Nevertheless, the oral bioavailability and BBB permeability of hydroxamic acid-based GCPII inhibitors are severely limited. Researchers have successfully identified an acetyloxybenzyl ester prodrug that, at a daily oral dose of 3 mg/kg (on a parent drug equivalent basis), exhibits analgesic effects equivalent to those of 10 mg/kg of the parent drug in a rat model of chronic compressive injury, achieving highly effective oral treatment for neuropathic pain [28]. Representative marketed neurological ester prodrugs are summarized in Table 1.

Table 1. Representative marketed ester prodrugs for neurological applications

Product Name	Prodrug Types	Indications	Mechanism Characteristics	References
Phenytoin (Cerebyx)	Phosphates	Status epilepticus, epilepsy	It is hydrolyzed by phosphatase to formactive phenytoin; it exerts its anticonvulsant effect by blocking voltage-dependent sodium channels.	[29]
Dimethyl fumarate (Tecfidera)	Dimethyl fumarate (Tecfidera)	Relapsing-remitting multiple sclerosis	Hydrolyzed to the active metabolite monomethyl fumarate, it activates the Nrf2 antioxidant pathway andupregulates Nrf2-dependent antioxidantgenes	[30]
Aripiprazole laurate (Aristada)	Long-Chain Fatty AcidEsters	Schizophrenia	It is hydrolyzed by enzymes to N-hydroxymethyl-aripiprazole, which isthen hydrolyzed to aripiprazole; aripiprazole is a partial agonist at D2/5-HT1A receptors and an antagonist at 5-HT2A receptors.	[31, 32]
Levodopa ethylester (etilevodopa)	Ethyl Esters	PD	Rapidly hydrolyzed to levodopa bynonspecific esterases in the gastrointestinal tract; improves gastricsolubility and shortens the time to peakconcentration	[33]

4. Translational applications of ester prodrugs in dermatology

The application of ester prodrug strategies in dermatology indicates their appropriateness for the special physiological and pathological features of the skin. By designing prodrugs rationally, they can not only overcome the basic obstacles in drug transport through the skin barrier but also adapt to the local microenvironment (like particular pH values or enzyme overexpression) to produce local and controlled activation, thus greatly enhancing the therapeutic effect and decreasing the systemic side effects. In this section, the recent progress in their translation to practical use will be reviewed from three aspects: the fundamentals of transdermal administration, disease-specific therapeutic uses, and formulation development.

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4.1. The skin barrier and transdermal delivery systems for ester prodrugs

The brick-and-mortar structure of the skin's stratum corneum is made up of keratinocytes and a lipid matrix mainly containing ceramides (about 40-50%), cholesterol (about 25%), and free fatty acids (about 10-15%), which together make up about 80-90% of the stratum corneum lipids and act as the main barrier to the transdermal drug absorption [34, 35]. Most of the pharmacologically active candidate molecules have polar groups like carboxyl and hydroxyl groups, resulting in their poor penetration through the lipid matrix of the stratum corneum [36]. Compared with other delivery methods, transdermal administration avoids the hepatic first-pass metabolism and the digestive enzyme degradation, allowing for the sustained and controlled release of the drug, thus reducing the frequency of the doses and improving the patient's compliance[37-39].

Esters function as prodrugs by shielding the polar groups temporarily and increasing lipophilicity, which greatly improves the trans- corneal stratum permeability. In recent years, the strategies for prodrug delivery across the skin have been continuously developed. The prodrugs tris(2-hydroxyethyl)butyl tranexamic acid (TA4) and tris(2-hydroxyethyl)butyl tranexamic acid ester (TA8) have been accumulated in pig skin at a level 2–3 times higher than the parent drug, and they are hydrolysed by endogenous esterases more than 90% within 2 hours [40]. However, the skin permeation rate of ketogluconate esters shows a parabolic relation with Log P, reaching its maximum at the propyl ester (46.61 nmol/cm²/h); longer alkyl chains decrease the permeation rate because of their low water solubility. This indicates that it is important to balance the lipophilicity and water solubility of the prodrugs in order to achieve high skin permeability [41-43].

4.2. Anti-inflammatory and immunomodulatory ester prodrugs

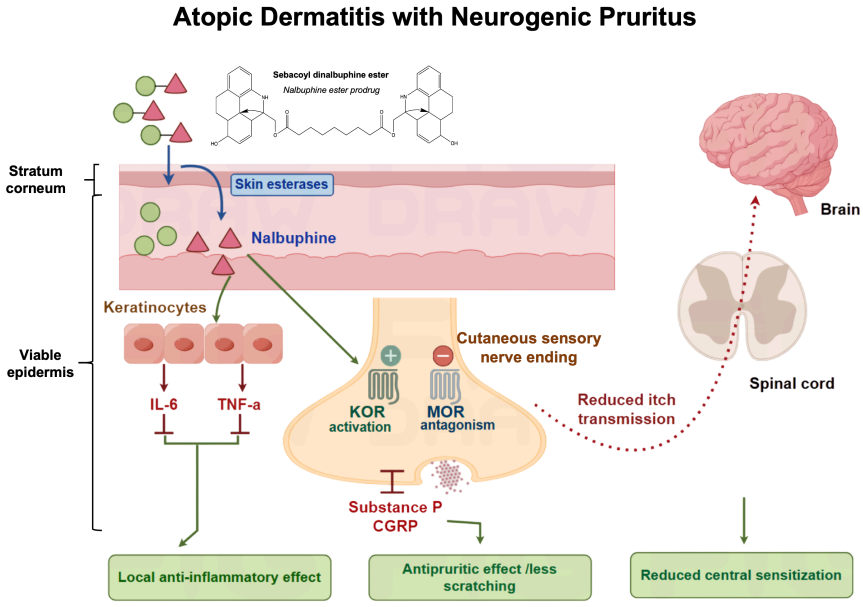


Figure 2. Atopic dermatitis with neurogenic pruritus

Note: After crossing the stratum corneum, the lipophilic nalbuphine ester prodrug is hydrolyzed by cutaneous esterases to release nalbuphine locally, thereby modulating opioid-receptor signaling and reducing neurogenic pruritus.

The treatment of various inflammatory skin conditions requires immune modulation and control of inflammation, requiring potent medications that act locally on the dermal tissues while minimizing

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systemic exposure [44, 45]. The topical application of nonsteroidal anti-inflammatory drugs and corticosteroids is often limited by inadequate penetration and skin irritation. In contrast, ester prodrugs enhance lipophilicity by masking ionization sites; after transdermal penetration, they are hydrolyzed by skin esterases to release the parent drug, thereby promoting local drug accumulation. Representative dermatological ester prodrugs are summarized in Table 2. The local activation and antipruritic mechanism of sebacoyl dinalbuphine ester is illustrated in Figure 2.

Table 2. Representative marketed ester prodrugs for dermatological applications

Product Name	Prodrug Type	Skin/Transdermal Indications	Mechanism of Action	References
Tazorac® (tazarotene)	Ethyl tazarotene	Psoriasis, Acne, Actinic Keratosis	Activated by hydrolysis by cutaneous esterases, selectively activates RARβ/γ	[46-50]
Myristyl nicotinate topical cream	Nicotinamide myristate	Prevention of Actinic Keratosis (Photoaging of the Skin)	Skin esterase-activated water releases niacin, which activates the niacin receptor (GPR109A), improves photoaging of the skin, and promotes DNA repair	[51, 52]
CU-30101	Ester-based local anesthetics	Anesthesia for Epidermal Surgery	Reversibly blocks voltage-gated sodium channels, providing rapid onset and long-lasting effects for epidermal anesthesia	[53]

5. Challenges, cutting-edge strategies, and prospects for translation

5.1. Major bottlenecks in the current development of ester prodrugs

5.1.1. Individual and species-specific differences in esterase expression and activity

At the species level, the tissue distribution and substrate selectivity of enzymes such as CES and AADAC involved in hydrolyzing prodrugs in humans differ fundamentally from those in commonly used laboratory animals, making it difficult to directly extrapolate activation data obtained from preclinical models to humans [54, 55]. Taking curcumin diethyl disuccinate as an example, its in vitro metabolic characteristics are similar in canine and human plasma but differ markedly from those in rat plasma. This observation demonstrates that selecting an appropriate preclinical animal model is crucial for accurately predicting human PK behavior [56].

5.1.2. Premature hydrolysis in plasma and formulation stability

The susceptibility of ester bonds to hydrolysis is both the basis for the activity of ester prodrugs and one of their main limiting factors. In the systemic circulation, if the kinetics of ester bond hydrolysis are not finely regulated by steric hindrance or electrostatic effects, prodrugs are highly susceptible to premature cleavage by plasma esterases or by hepatic first-pass metabolism in the liver before they can cross the BBB or the stratum corneum. This not only reduces the effective concentration in the target tissues but also increases the likelihood of systemic toxicity caused by the peripheral accumulation of the parent drug [13, 57].

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5.1.3. Safety of leaving groups

During esterase-mediated hydrolysis, ester prodrugs release not only the active parent drug but also leaving groups derived from the esterified moiety [58]. Though groups leaving usually do not affect pharmacological action, their metabolic stability, in vivo concentration, and possible toxicological effects may influence the overall safety of the prodrug [59]. For the purpose of administering long-term medication against neurological and skin diseases, the total amount of groups leaving and the danger of chronic toxicity should be given special attention.

5.2. The path from the laboratory to clinical practice

5.2.1. Application of physiologically based pharmacokinetic (PBPK) models in the clinical development of ester prodrugs

By combining physiological parameters like organ volume and blood flow, as well as the expression levels of esterases in different tissues, PBPK models can depict the in vivo processes of both prodrugs and their active metabolites separately, offering a quantitative approach to generalize the preclinical data of ester prodrugs to human beings. For MGS0274, CES1 was identified as the main esterase responsible for hydrolytic activation; in vitro enzyme kinetic parameters, animal pharmacokinetics data, and human tissue esterase distribution were then used to establish a PBPK model, which could precisely predict the plasma concentration-time curves of the prodrug and its active metabolite MGS0008 after a single oral dose in healthy subjects [60]. On top of that, PBPK models also serve as a reasonable basis for the iterative development of dosage forms of ester prodrugs. For example, a PBPK absorption model was employed to simulate the clinical pharmacokinetics of an immediate-release formulation of LY545694, and it was applied to deduce the important design parameters for a sustained-release formulation, thus guiding the further development process [61].

5.2.2. Key considerations for clinical trial design

Clinical trials should test the prodrug delivery and the tissue-specific activation. The bioavailability tests should investigate the prodrug and its active metabolites' profiles and should study the relation between their exposure, not only the area under the curve (AUC) and the maximum concentration (Cmax) of the parent drug [60, 61]. For CNS and skin targets, the peripheral blood concentrations cannot reflect the exposure to the target tissues. Neurological trials can use the BBB penetration, intracerebral distribution, and target engagement by means of cerebrospinal fluid sampling and dynamic PET imaging [62, 63]. In dermatological trials, skin biopsy or microdialysis can be applied to examine the stratum corneum penetration and the specific enzyme release [64].

Individual differences in the activity of cholinesterase and genetic polymorphisms may affect the prodrugs with a narrow therapeutic index, so it is important to include esterase genotyping or phenotypic analysis prospectively in the early-phase clinical trials for personalized dosing guidance [65, 66]. For prodrugs that are hydrolyzed in the gastrointestinal tract or have a narrow absorption range, the release pattern of the drug should be optimized based on the distribution of intestinal esterases and the absorption site to guarantee the release at the optimal position and efficient activation [61, 67].

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6. Conclusion: a comparison of the design advantages and application areas of ester prodrugs

By masking polar functional groups and undergoing esterase-mediated activation, ester prodrugs can modify membrane permeability and decrease systemic toxicity. In neurological applications, attention is paid to brain barrier penetration and transport system utilization, while in dermatological applications, emphasis is on stratum-corneum penetration, local accumulation, and controlled release.

Future progress should concentrate on safer promoieties, dependable esterase activation, and preparation techniques that maintain prodrug stability and facilitate selective release in tissues.

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