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PRODRUG STRATEGIES TO IMPROVE ORAL BIOAVAILABILITY OF POORLY PERMEABLE DRUGS

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Abstract

Many pharmacologically active molecules fail as oral drugs because they are too polar, too charged or too readily effluxed to cross the intestinal epithelium. Prodrug design addresses this by attaching a removable promoiety that improves absorption and is shed after uptake. This narrative review summarises published work on ester and carbamate masking, amino acid and other transporter-targeted prodrugs, and phosphate and phosphonate prodrugs, with marketed examples such as valacyclovir, dabigatran etexilate and tenofovir alafenamide. It also covers enzymatic activation, evaluation methods and development pitfalls. The literature shows consistent gains for well-chosen designs but also recurring problems with stability, variability and toxicity of promoieties. This is a review of published literature and reports no new experimental data.

1. INTRODUCTION

Taking a tablet is still the preferred way to give most drugs, but the gut wall is a selective barrier. Molecules that dissolve well in water but carry charges or many hydrogen-bonding groups often cross it poorly, while those that cross it easily may not dissolve. Some of the most potent enzyme inhibitors, nucleotide analogues and antibiotics were nearly abandoned for this reason. Chemists have two broad answers. One is to redesign the molecule, accepting that potency or selectivity may suffer. The other is to leave the active core untouched and attach a temporary group that handles the transport problem, which is the idea behind a prodrug [1, 2].

The term goes back to Albert, who used it in 1958 for compounds that are inactive until converted in the body into the active agent [3]. Early examples were found by accident,

and the rationale was often worked out afterwards [4]. Today prodrugs are designed deliberately, and a considerable share of newly approved small-molecule drugs in recent years have been prodrugs [2]. Their aims vary: better solubility, improved permeability, longer duration, targeted delivery or reduced toxicity [1, 5]. This review concentrates on one aim, improving oral absorption of drugs that are poorly permeable, and on the chemical strategies used to achieve it.

The conceptual foundations were laid down well before the modern wave of marketed products. Bundgaard's edited volume, Design of Prodrugs, collected the chemistry of masking carboxyl, hydroxyl and amino groups in the mid-1980s, and much of what is now routine, from acyloxyalkyl esters to Mannich bases, was already described there [6]. What has changed since is the tooling: knowledge of intestinal transporters and metabolising enzymes, better in vitro models and a clearer view of how absorption, first-pass loss and activation interact. This has moved prodrug design from a chemical exercise towards a biopharmaceutical one, in which the question asked first is where the barrier lies [4, 6].

A prodrug is not simply a more lipophilic version of the parent. It must remain intact long enough to cross the epithelium, be converted quickly and completely once absorbed, and release a promoiety that is itself safe. Those requirements pull in different directions. A group that is stable in gastric fluid may be too stable in plasma, while one that is cleaved readily by intestinal esterases may release the parent in the gut lumen, where the polar drug cannot be absorbed [7, 8]. Success rests on a match between chemistry, enzyme distribution and the physiology of absorption, and much of the literature reviewed here concerns that match.

A final scope note. Prodrugs that improve aqueous solubility, such as phosphate esters of poorly soluble drugs, and those that modify duration or target specific tissues are covered only where they bear on oral absorption. Readers interested in solubility-oriented approaches are referred to the reviews by Stella and Nti-Addae and by Müller [5, 9]. Prodrugs for the central nervous system, in which lipophilicity must be tuned to cross the blood-brain barrier, raise further issues of their own that are discussed in the work of Anderson [10].

2. BARRIERS TO ORAL ABSORPTION

The physicochemical rules of oral absorption are well known. Egan and colleagues showed that human intestinal absorption could be separated into good and poor groups using little more than polar surface area and calculated lipophilicity, with a high polar surface area counting heavily against absorption [11]. These are rules of thumb, and many marketed drugs break them, especially natural products and substrates of transporters. Still, they capture the intuition that size and polarity limit passive diffusion across a lipid membrane. Varma and colleagues later analysed human absorption and first-pass elimination data to map the property space in which oral bioavailability is most likely [12].

The Biopharmaceutics Classification System places drugs in four classes by solubility and permeability, and its later extension to disposition adds the role of metabolism and transporters [13]. Class III drugs are soluble but poorly permeable, and class IV drugs are poor in both. Prodrug design for permeability is mostly directed at class III and, with a combined approach, class IV. Examples include acyclovir, a nucleoside analogue with limited and variable oral absorption, and carboxylic acid drugs such as the angiotensin-converting enzyme inhibitor diacid forms, which are ionised across the intestinal pH range [7, 13]. The classification offers a useful starting point, but permeability measurements for borderline compounds depend heavily on the method used.

Charge deserves its own comment. Carboxylic acids, phosphonates, sulfonates and amidines are ionised across most of the intestinal pH range, and an ionised molecule crosses a lipid membrane poorly, often by several orders of magnitude less than its neutral form. This is why so many of the polar drugs discussed in this review carry these groups. The ionisable group is usually also essential for binding to the target, such as

the carboxylate of an angiotensin-converting enzyme inhibitor or the amidine of a thrombin inhibitor, which is why it cannot simply be removed from the structure [7, 14]. Masking the group temporarily, and restoring it after absorption, is the logic of the prodrug approach.

Several biological factors compound the physical ones. The unstirred water layer and mucus slow the approach of drugs to the epithelium. Efflux transporters, such as P-glycoprotein, pump absorbed molecules back into the lumen. Enzymes in the enterocyte, particularly cytochrome P450 3A4, metabolise drugs during the first pass, and hepatic extraction takes a further share before the drug reaches the systemic circulation [12, 15]. A polar nucleotide analogue may thus face poor passive permeation, efflux and degradation by gastrointestinal enzymes in turn. Prodrug design can address several of these at once, since masking the polar groups both raises passive permeability and may reduce recognition by efflux pumps [15, 16].

The stomach and gut also create chemical hazards. Gastric acid can hydrolyse acid-labile groups, intestinal esterases and peptidases cleave ester and amide bonds, and bacterial enzymes in the colon attack many structures. A prodrug that is cleaved too early in the lumen releases the poorly absorbed parent where it cannot be taken up, which wastes the design [7, 8]. Beaumont and colleagues noted the practical challenge for the discovery chemist: a prodrug has to be stable enough in the gut to cross, but unstable enough in blood and liver to release the parent, and the two environments are closer in enzyme content than one would like [7].

Absorption of a polar drug is often a matter of the route taken as much as the size. Small hydrophilic molecules may cross by the paracellular pathway through tight junctions, but this route is limited by the pore size and is easily saturated, so only a small fraction of the dose moves this way. Transcellular passive diffusion requires lipophilicity, and carrier-mediated transport requires structural resemblance to a natural substrate. Prodrug strategies map onto these routes. Masking polarity aims at transcellular diffusion, while attaching amino acids or other nutrient mimics aims at carriers, and the choice depends on what the parent drug will tolerate chemically [16, 17].

3. ESTER AND CARBAMATE PRODRUGS

Esters are the most common prodrug type. A carboxylic acid or alcohol on the parent is converted to an ester, which removes a charge or a hydrogen-bond donor, increases lipophilicity and, after absorption, is cleaved by esterases abundant in the intestinal wall, liver and blood [8, 18]. The statistical weight of the approach is clear from reviews of marketed prodrugs, in which esters make up a large proportion [2, 8]. Testa and Mayer's text on hydrolysis in drug and prodrug metabolism gives the chemical and enzymological background: the rate of cleavage depends on the steric and electronic properties of both the acid and alcohol parts, so it can be tuned across a wide range [18].

Choice of promoiety is a design variable with consequences beyond lipophilicity. Small alkyl esters such as ethyl are cleaved at moderate rates and release ethanol, which is harmless in the quantities involved. Larger or more branched esters hinder esterase attack and slow release, while esters of amino acids or sugars carry additional transport properties [8, 18]. Stella has emphasised that a prodrug should be seen as part of a development strategy and not merely a chemical modification, since the promoiety affects stability, formulation, manufacturing and regulatory classification as well as absorption [19]. The best candidates are those where the promoiety is cheap, safe and predictably cleaved.

Enalapril is a typical case. The active diacid, enalaprilat, is poorly absorbed after oral dosing because of its two ionised carboxyl groups, while the ethyl ester is absorbed much better and is converted to the active form by hepatic esterases [7, 8]. Oseltamivir follows the same pattern: the ethyl ester of an active carboxylate neuraminidase inhibitor, absorbed well and converted extensively to the active metabolite after oral dosing [20]. Cefuroxime axetil is a cephalosporin esterified with an acetoxyethyl group; it is

absorbed from the gut and hydrolysed by esterases in the intestinal mucosa, and its absorption is influenced by food [7, 21].

The acyloxyalkyl esters, in which an acyloxymethyl or acyloxyethyl group links the acid to the promoiety, deserve a mention because they are cleaved in two steps, first by an esterase and then by spontaneous breakdown of the unstable intermediate with release of an aldehyde. Pivoxil and axetil esters follow this route. The advantage is that the esterase attacks an unhindered ester some distance from the parent, so cleavage is fast even where the parent is bulky. The disadvantage is the formation of formaldehyde or other aldehyde and a carboxylic acid such as pivalic acid, which have raised concerns about long-term effects such as carnitine depletion with pivalate-containing prodrugs [1, 8].

Dabigatran etexilate illustrates how far an ester strategy can go. Dabigatran itself is a highly polar amidine that is poorly absorbed, so it is dosed as a double prodrug, with the amidine masked as a carbamate and the carboxylic acid as an ethyl ester. After absorption, carboxylesterases in the intestine and liver cleave both groups to release the active drug [14, 22]. Absolute bioavailability is nevertheless low, in the order of a few per cent, which gives some idea of how bad the parent is. The example shows that prodrugs can make absorption feasible without making it efficient, and that large variations in a small bioavailability can matter clinically [14].

Carboxylesterases are central to ester prodrug activation, so differences in their distribution matter. Human carboxylesterase 1 is abundant in the liver and acts on esters with a small alcohol group and large acyl group, while carboxylesterase 2 is the dominant form in the intestine and prefers the opposite arrangement [22]. This means that the design of an ester determines where it is activated: a prodrug that is a CES2 substrate may be hydrolysed in the enterocyte during absorption, and one that is a CES1 substrate will largely survive until it reaches the liver. Both outcomes can be useful, but they should be intended and not left to chance [7, 22].

Carbamates and amides are more stable than simple esters and are used when slower or enzyme-specific release is wanted. N-acyloxyalkoxycarbonyl groups, N-Mannich bases and amino acid amides have all been explored as masks for amines, amidines and hydroxyl groups [1, 5]. Their stability can be a problem when conversion is too slow to be useful, and few amide prodrugs achieve complete release in humans. Where an amidine or guanidine must be masked, as in dabigatran, carbamate formation is a practical option because direct esterification is not available [4, 14]. For amines, the choice often falls to an amino acid conjugate, which leads on to transporter-targeted designs.

4. TRANSPORTER-TARGETED PRODRUGS

Passive masking is not the only choice. Drugs can be disguised as nutrients so that they are carried across the gut wall by transporters that normally absorb amino acids, peptides, vitamins or sugars. Han and Amidon described the principle: a promoiety is chosen not only to alter lipophilicity but also to make the prodrug a substrate of an intestinal carrier, which then provides a high-capacity entry route [17]. Majumdar and colleagues reviewed transporter and receptor-targeted prodrug design for human and veterinary drugs, and Dahan and colleagues updated the approach for oral delivery [15, 16]. The attraction is that absorption becomes less dependent on lipophilicity.

The peptide transporter PepT1 is the best-studied target. It is expressed at the brush border of the small intestine, takes up di- and tripeptides, and has a wide tolerance for structures that resemble them, including some drugs such as beta-lactam antibiotics and angiotensin-converting enzyme inhibitors [23]. Brandsch reviewed drug transport via this carrier and noted its low affinity but high capacity, features that suit absorption of large doses [23]. These properties make PepT1 attractive to the prodrug designer, who can attach an amino acid to a polar drug and hope that the resulting conjugate is recognised as a substrate [17, 23].

The structural logic of the peptide transporter is worth spelling out. PepT1 recognises substrates with a free or substituted amino group and a carboxyl or carboxyl-like group

separated by a short distance, and it tolerates a wide variety of side chains. L-Valine, with its branched aliphatic side chain, was found in affinity studies to give favourable recognition, which probably explains why valyl esters feature so often among published prodrugs [17, 23, 24]. Esters of other amino acids, including isoleucine and phenylalanine, have also been tested, and stereochemistry matters, with L-forms preferred over D-forms. These structure-transport relationships are a practical basis for choosing a promoiety once PepT1 has been selected as a target [17, 23].

Valacyclovir is the success story. Acyclovir is a potent antiviral whose oral bioavailability is low and variable, in the range of about a fifth or less of the dose. The L-valyl ester, valacyclovir, was found to be a substrate of the intestinal and renal peptide transporters PEPT1 and PEPT2 [24]. After oral dosing in volunteers, valacyclovir is rapidly converted to acyclovir, and the absolute bioavailability of acyclovir rises to roughly half of the dose, several times higher than with acyclovir itself [25, 26]. The conversion is by first-pass hydrolysis in the intestine and liver. Dose proportionality over the range of clinical interest was shown in early volunteer studies [25].

The valacyclovir example has had a lasting influence. It showed that an amino acid ester can improve absorption of a nucleoside analogue through a carrier that the parent barely used, and it prompted similar designs for other antivirals and for anticancer nucleosides [16, 17]. Not all attempts have worked. Affinity for the carrier is often lost when the amino acid is attached to a bulky parent, and activation by hydrolysis may be too slow or occur at the wrong site [15, 17]. Even valacyclovir needs dosing adjustment in renal impairment because of the effect on its elimination and that of acyclovir, so a successful prodrug does not remove all complexity [26].

Gabapentin enacarbil takes a different approach. Gabapentin is absorbed by a saturable amino acid transport system in the upper small intestine, so its bioavailability falls as the dose rises. Cundy and colleagues designed a prodrug, gabapentin enacarbil, that is a substrate of high-capacity transporters expressed throughout the gut, including the monocarboxylate transporter MCT-1 and the sodium-dependent multivitamin transporter SMVT, and is converted to gabapentin by esterases [27]. In this case the prodrug was aimed at reducing dose dependence and the regional limitation of absorption rather than at passive permeability. This broader view of what a prodrug can fix is a useful reminder that low bioavailability has several causes [16, 27].

Transporter targeting is attractive in principle but has pitfalls. Transporter expression varies between individuals and along the gut, and may be affected by diet and disease. Competition with dietary peptides can reduce uptake of a PepT1 substrate. Animal models may overstate the picture, because rodent and human transporters differ in affinity [15, 23]. Some of the gains reported in cell-based assays have not carried over to humans. Reviewers therefore recommend confirming transport using human-derived models and, where possible, human data early in development, so that investment is not made in a mechanism that works only in the laboratory [16, 17].

5. PHOSPHATE AND PHOSPHONATE PRODRUGS

Phosphonates and phosphates pose a near-extreme permeability problem. At physiological pH, a phosphonic acid carries two negative charges, so acyclic nucleoside phosphonates are barely absorbed after oral dosing and can enter cells only slowly [28, 29]. Yet their pharmacology is attractive: the phosphonate group is a stable mimic of the monophosphate and bypasses the first, often rate-limiting, phosphorylation step. De Clercq and Holý described the class of acyclic nucleoside phosphonates as a key group of antivirals, and masking the phosphonate is what turned them into oral drugs [28]. Wiemer and Wiemer reviewed the prodrug chemistry used for this purpose [29].

Tenofovir disoproxil fumarate (TDF) is the established example. The diphosphonate charges are masked with two isopropyloxycarbonyloxymethyl groups, which are removed by esterases and chemical

breakdown to release tenofovir. Studies of related prodrugs in dogs showed that the bis-ester was absorbed far better than the parent phosphonate, with plasma tenofovir obtained after oral dosing [30]. TDF became a mainstay of antiretroviral and hepatitis B therapy. Its weakness is that conversion happens largely in the gut and plasma, so the circulating tenofovir concentration is higher than needed for the target cells, with associated renal and bone effects reported during long-term use [28, 30].

Tenofovir alafenamide (TAF) was designed to correct this. It is a phosphonoamidate in which the phosphonate is masked with an aryl group and an amino acid ester, a design that is relatively stable in plasma but is taken up by cells and cleaved intracellularly. Cathepsin A was identified as the major hydrolase catalysing the first intracellular step, and metabolism studies of the compound in blood showed good plasma stability [31, 32]. The practical result is higher intracellular concentration of the active diphosphate in target cells, at lower circulating tenofovir levels, allowing a much smaller dose than TDF [31, 32]. This is an example of oral prodrug design merging with cell-targeted design.

One lesson from phosphorus-based prodrugs is that the site of activation can matter more than the extent of absorption. TDF is largely converted before it reaches target cells, so tenofovir is exposed to the kidney, while TAF survives in plasma and is activated within cells [30, 31, 32]. In effect the design moves the activation step from the circulation to the target tissue. The lesson applies beyond antivirals: for any prodrug aimed at a specific tissue, activation enzymes in that tissue should be identified early, and plasma stability should be treated as a design requirement and not just a convenience [31, 33].

The phosphoramidate approach has become known as the ProTide technology, and Mehellou and colleagues reviewed its development from concept to clinic [33]. The sofosbuvir story is the best-known application. The parent nucleoside monophosphate cannot be dosed because it is too polar, so a phosphoramidate was designed that enters hepatocytes, is converted by esterase and phosphoramidase activity to the monophosphate and is then phosphorylated further to the active triphosphate [33, 34]. Sofosbuvir, then known as PSI-7977, was selected in discovery work for its potency against hepatitis C virus and favourable properties, and transformed the treatment of that infection [34]. Both TAF and sofosbuvir show that a prodrug can solve more than absorption.

A simpler case is the phosphate ester used to raise solubility. Phosphate monoesters of poorly soluble drugs are hydrolysed by alkaline phosphatase at the brush border, releasing the parent for absorption, as Fleisher and colleagues noted in their review of solubility-limited oral delivery [35]. Fosamprenavir, the phosphate ester of the HIV protease inhibitor amprenavir, belongs to this group. The approach works best when the parent is permeable but dissolves too slowly. It can backfire if the released parent supersaturates and precipitates before it is absorbed, a risk analysed in work on enzyme-mediated precipitation of parent drugs from phosphate prodrugs [35, 36].

The published evidence on these strategies is organised in table 1, which sets marketed or well-studied examples against the chemical approach and the reported effect on absorption or delivery. The spread of entries across design groups is shown in fig. 1. Ester prodrugs dominate the table, which mirrors their dominance among marketed drugs, but the phosphorus-based and transporter-targeted entries account for much of the innovation of the last two decades. The table is a synthesis of published findings; it does not rank the approaches, since each solves a different problem [1, 2, 8].

6. EVALUATION AND DEVELOPMENT

A prodrug programme needs evaluation tools suited to a two-step process. Chemical stability is tested in buffers across the gastrointestinal pH range and in simulated gastric and intestinal fluids. Enzymatic conversion is studied in intestinal and liver homogenates, microsomes, S9 fractions, plasma and purified esterases, which show where and how quickly the prodrug is

activated [7, 18]. Species differences are a concern because esterase activity in rodent plasma is much greater than in human plasma, so a prodrug that appears unstable in rat plasma may be perfectly stable in humans. Beaumont and colleagues cautioned against reliance on rodent data for ester prodrugs for this reason [7].

Table 1: Representative prodrug strategies for improving oral absorption of poorly permeable drugs

Prodrug (parent)	Strategy and reported effect on absorption or delivery	Ref.
Enalapril enalaprilat	Ethyl ester masks a carboxylate; absorbed far better than the diacid and hydrolysed in the liver.	[7, 8]
Cefuroxime axetil cefuroxime	Acetoxyethyl ester absorbed in the gut and cleaved by mucosal esterases; absorption affected by food.	[7, 21]
Oseltamivir oseltamivir carboxylate	Ethyl ester of a polar carboxylate; well absorbed and extensively converted to the active form.	[8, 20]
Dabigatran etexilate dabigatran	Double prodrug masks an amidine and an acid; activated by carboxylesterases but bioavailability remains low.	[14, 22]
Valacyclovir acyclovir	L-valyl ester recognised by peptide transporters; raises acyclovir bioavailability several-fold.	[24, 25, 26]
Gabapentin enacarbil gabapentin	Substrate of high-capacity transporters; reduces dose-dependent absorption of gabapentin.	[16, 27]
Tenofovir disoproxil tenofovir	Bis-carbonate ester masks both phosphonate charges and gives oral absorption.	[28, 30]
Tenofovir alafenamide tenofovir	Phosphonoamidate cleaved intracellularly by cathepsin A; high target-cell levels at low plasma levels.	[31, 32]
Sofosbuvir nucleoside monophosphate	ProTide design delivers a monophosphate into hepatocytes where the parent cannot enter.	[33, 34]
Phosphate esters of poorly soluble drugs	Hydrolysed by brush-border alkaline phosphatase; precipitation of the released parent is a risk.	[35, 36]

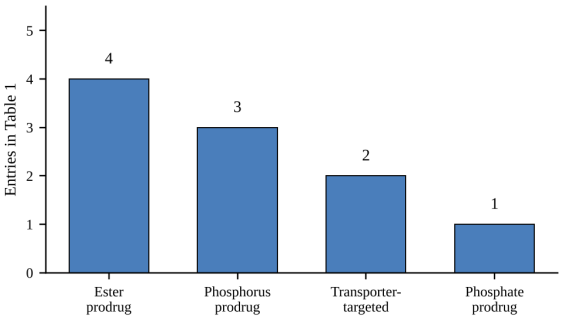


Fig. 1: Number of entries in table 1 by prodrug strategy

Permeability is assessed with Caco-2 monolayers, parallel artificial membrane assays, and in situ perfusion or isolated tissue models. Caco-2 cells express carboxylesterases at lower levels than the human intestine, so ester prodrugs may appear more stable in the assay than in vivo, and the resulting permeability can be misleading [7, 16]. The assay is nevertheless the usual first screen for transporter substrates, where uptake is compared with and without a competing substrate or inhibitor. Such experiments, with uptake in transporter-expressing cells, provided the early evidence for the PepT1 recognition of valacyclovir [23, 24].

Formulation interacts with prodrug performance in ways that are easily missed. Excipients can alter local pH and thereby change chemical stability, some surfactants inhibit esterases or efflux pumps, and dissolution rate determines how much prodrug is present at the absorptive surface at one time [9, 35]. For prodrugs of poorly soluble parents, supersaturation and precipitation of the released parent may limit gains, so formulation work should be done in step with chemistry and not afterwards [9, 36].

Animal pharmacokinetics are informative but must be read carefully. The dog has been widely used for phosphonate prodrugs, as in

the early studies of tenofovir prodrugs [30], but species differ in esterase activity, transporter expression and first-pass metabolism, so absolute bioavailability does not scale directly to humans. Measuring both the prodrug and the parent in plasma is essential, because the parent concentration can come from conversion in the gut wall, liver or blood, and the ratio gives a clue to where activation occurs [7, 30]. Intact prodrug in the portal vein indicates that it survives the gut wall, while parent in the portal vein implies enterocyte conversion [7, 8].

Clinical development raises its own questions. Variability in activation, due to genetic differences in carboxylesterases, food effects and drug interactions with esterase inhibitors, can lead to variable exposure to the active drug [21, 22]. Cefuroxime axetil absorption is increased by food [21], and dabigatran etexilate exposure is affected by P-glycoprotein inhibitors because the prodrug is an efflux substrate [14]. Both illustrate that prodrugs add a second set of interaction and variability mechanisms to those of the parent. Dose-finding therefore needs to consider the prodrug, the parent and the promoiety, and bioequivalence studies are normally based on the active moiety [2, 14].

Pharmacogenetic and disease effects can alter prodrug activation. Genetic variants of carboxylesterase 1 have been linked to altered activation of ester prodrugs, and liver disease may reduce enzyme levels and slow conversion [22]. Intestinal disease, such as inflammatory bowel disease, changes transporter and enzyme expression and can alter absorption in ways that are not captured in healthy volunteer studies [22, 23]. In practice these effects are rarely quantified before approval, and are discovered later through case reports or pharmacovigilance. The point for development teams is that a prodrug adds biological uncertainty, which should be tested in relevant subgroups where it is plausible [2, 22].

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limits on the literature need to be kept in mind. Many published prodrug studies stop at in vitro permeability or animal pharmacokinetics, and few report human data, so claims of improved bioavailability rest largely on preclinical models. Failed prodrugs are rarely published, and the successes that appear in reviews are a selected sample [2, 19]. In addition, the success of a handful of landmark examples such as valacyclovir and tenofovir alafenamide may encourage an overly optimistic view of how readily a given polar drug can be converted into an orally useful one [4, 19].

There are scientific gaps as well. Enzyme expression in human intestine, including that of carboxylesterases, peptidases and phosphatases, is incompletely mapped, particularly along the length of the gut and in disease [7, 22]. Predictive models of prodrug absorption and activation are still crude, and in vitro to in vivo extrapolation for the two-step process is not reliable. Interactions with the gut microbiome, whether a prodrug is metabolised before it reaches the absorptive surface, have received little attention. These gaps explain why prodrug design is still partly empirical [16, 19].

8. CONCLUSION

Prodrugs offer a proven route around the intestinal barrier for polar drugs. Ester and carbamate masking raises passive permeability and relies on abundant esterases for activation, as enalapril, oseltamivir and dabigatran etexilate show [8, 14, 20]. Transporter-targeted designs such as valacyclovir turn uptake carriers into an entry route [24, 25], and phosphonate and phosphoramidate prodrugs have made previously unabsorbable nucleotide analogues into oral drugs [28, 33].

The evidence also shows where the approach is weak. Activation depends on enzymes whose distribution varies between species and individuals, the released promoiety must be safe, and bioavailability can stay low despite a clever design [7, 14, 22]. Much of the supportive data is preclinical, and failures are underreported [2, 19]. For drug developers, the practical lesson is to define the barrier first, choose the strategy that addresses it, and test activation and transport in human-relevant systems early [16, 17].

9. ABBREVIATIONS

BCS-Biopharmaceutics Classification System, CES-Carboxylesterase, HIV-Human immunodeficiency virus, MCT-1-Monocarboxylate transporter 1, PepT1-Peptide transporter 1, SMVT-Sodium-dependent multivitamin transporter, TAF-Tenofovir alafenamide, TDF-Tenofovir disoproxil fumarate

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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