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Original Article

Innovations In Prodrug Approaches For Enhanced Bioavailability

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ABSTRACT

Background: Bioavailability has long been one of the major drug development issues, and it is estimated that more than 40% of novel chemical entities are unsuccessful because of bad pharmacokinetic characteristics. Prodrug strategies are advanced strategies of bypassing the bioavailability constraints through temporary changes of the drug molecules to improve drug absorption, distribution and therapeutic effects.

Objective: This work discusses recent advances in prodrug design and development with particular attention paid to new strategies that help increase oral bioavailability, tissue-targeting strategies, and overcome physiological barriers. We examine new strategies such as carrier mediated prodrugs, enzyme mediated systems and nanotechnology mediated approaches.

Methods: To carry out a literature review, PubMed, Web of Science, and SciFinder databases were searched involving publications published since 2015. The search terms found such as prodrug design, bioavailability enhancement, drug delivery, and similar terms. It focused on the clinically validated methods and future technologies that had translational potential.

Results: New advances show that prodrug design has been advanced in the following ways: transporter-targeted prodrug designs are based on exploitation of endogenous uptake processes, stimuli-responsible prodrug designs have the ability to be site-specifically activated, and combination prodrug designs can include multiple bioavailability limitations simultaneously. Case studies indicate that bioavailability has been enhanced between 2 and above 20 folds than parent drugs.

Conclusion: The current methods of prodrug are finally developed and flexible tools of improving drug bioavailability. Combined with computational design, mechanism of absorption barriers, and sophisticated chemical approaches the prodrug toolkit keeps growing to able to provide solutions to more and more challenging drug candidates.

Keywords: prodrug, bioavailability, drug design, pharmaceutical chemistry, drug delivery, targeted therapy.

INTRODUCTION

The idea of prodrugs, biologically inactive analogs of active drugs that can be converted to give the Eactive parent drug in vivo, has developed through a complex strategy of enhancing solubility of drugs to an elaborate pharmaceutical solution to several drug development and delivery issues. With the discovery of how about 10 per cent of the drugs approved are prodrugs, pharmaceutical scientists have been adopting this approach as a potent means of overcoming the pharmacodynamics and pharmacokinetic drawbacks.[1]

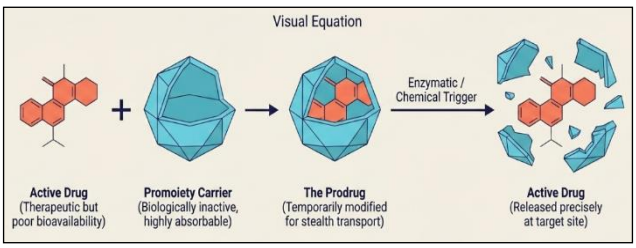

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Figure 1. Basic concept of prodrug design

Bioavailability, defined as the fraction of an administered dose that reaches systemic circulation in unchanged form, represents a critical determinant of drug efficacy and safety. For orally administered drugs, bioavailability is influenced by multiple factors including solubility, permeability across biological membranes, metabolic stability, and susceptibility to efflux transport. The Biopharmaceutics Classification System (BCS) categorizes drugs based on solubility and permeability characteristics, with BCS Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) drugs presenting particular challenges for achieving adequate bioavailability.[2]

Formulation techniques that have been used to improve bioavailability in traditional methods have been particle size reduction, salt formation, and excipient complexation. Although these techniques are still useful, they can frequently be inadequate with highly lipophilic compounds, drugs with a large extent of first-pass metabolism, or molecules that are efflux transporter substrates. The prodrug solutions are complementary or alternative solutions in that they essentially modify the properties of the drug at the absorption stage but retain its therapeutic potential on activation.[3]

The recent developments in the knowledge of the absorption mechanisms, the biology of the transporters and the metabolic pathways have allowed more rational design of prodrugs. This has resulted in carrier-targeted prodrugs that utilise endogenous uptake capabilities and was made possible by the identification of certain transporters that are expressed in intestinal epithelium. On the same note, the development of the knowledge of the expression patterns of this enzyme in various tissues has enabled the development of tissue-specific prodrugs, which are selectively activated at the target location.[4]

The variety of promoieties that have been designed to be used in prodrug construction has increased with innovations in chemical synthesis and analysis techniques. In addition to straightforward ester and amide linkages, recent prodrug approaches incorporate sophisticated chemical designs such as cyclic designs, self-immolative linkers and stimuli-responsive groups that allow the activation kinetics and location to be precisely controlled. Combination of computational modeling with experimental validation has enhanced optimization of prodrugs, whereby, prediction of physicochemical properties, metabolic stability and transporter interactions can be made.[5]

This work will discuss the current developments in prodrug strategies to improve bioavailability, classified by mechanism and use. Our areas of interest include those strategies which have shown clinical or preclinical efficacy, new technologies with translational potential and underlying principles that inform contemporary prodrug design. The aim is to offer a complete picture of the latest prodrug strategies and future outlook of this dynamic area to pharmaceutical scientists and medicinal chemists.[6]

1. Classification of prodrug:

1.1 Carrier linked prodrug

Prodrugs formed as carrier-linked probothermal include chemically binding an active drug molecule to a promotory (carrier group) by a breakable group. This conjugation is supposed to be stable enough when in a physiological environment, such that, once administered, it may be broken by an enzyme or a chemical into liberating the active parent drug in vivo.[7]

This method is especially practical when dealing with drugs the application of which as a therapeutic agent is hampered by undesirable physicochemical characteristics of low solubility, low permeability or lack of stability. These properties can be altered temporarily, though by conjugating the drug with an appropriate carrier group, without changing the underlying pharmacological activity of parent compound. After cleavage of the prodrug in the body, the active drug is again synthesized, and it produces the desired effect on the body.[8]

A perfect carrier group needs to be non-toxic and biologically inactive and readily removed out of the body once the drug is released. The choice of the promoiety is very important as it dictates the stability, rate of activation and the overall activity of the prodrug.[9]

The dipivalyl ester of epinephrine using is a classic example of this type of drugs being used, as it enhances corneal tissue penetration and minimizes loss of bioactivity of the medication due to rapid metabolism, which increases systemic side effects.[10]

Carrier-linked are classified into based on the nature and the activation mechanism.

1. Cascade-Latentiated Prodrugs: The prodrugs then go through series of enzymatic changes with each conversion, resulting in the first conversion stage which gives an intermediate prodrug, which is further broken down to release the active drug.[11]

2. Double Prodrugs : To be activated, double prodrugs need two-step activation. The compound given is first changed into some intermediate form that is metabolized into giving the active drug.[12]

3. Macromolecular Prodrugs: Here, the drug is coupled to huge carrier molecules that enhance drug stability, delays the rate of circulation and allows controlled release of drug.[13]

4. Site-Specific Prodrugs: They are used to transport a drug to a certain tissue or organ. Activation is selective to the target site owing to the existence of particular enzymes or environmental conditions leading to a high efficacy and low toxicity in therapy. This would be most advantageous where there is cancer and localized infections.[14]

1.2 Bioprecursor Prodrug

Bio precursor prodrugs are such substances which lack a carrier (promoiety) group. Rather, they are created by a structural alteration of the active drug itself, and are transformed into the active form via a metabolic/chemical change in the body.[15]

Bioactivation of bioprecursor prodrugs does not happen through the cleavage confluence of a linkage as in the case of carrier-linked prodrugs. Instead, the molecule already contains an inactive functional group (or inactive form of the active group), so-called latent functional group, which is changed to the pharmacologically active species, through biochemical reactions.[16]

Such changes often entail:

- Oxidation
- Reduction
- Phosphorylation

Oxidative Bioactivation

Oxidative reactions are an important route of activation of bioprecursor prodrugs. Making the inactive compound active is done, in this process, by metabolic enzymes (mainly in the liver) which oxidize the inactive compound to its active counterpart.[17]

An example in point is the well-known nabumetone, a nonsteroidal anti-inflammatory drug (NSAID). Nabumetone, unlike most of the NSAIDs, has no free carboxylic acid group that is usually the cause of gastric irritation. This leads to less pain in the stomach. It is oxidatively metabolized and on being absorbed in the intestine, it will be converted to the active acidic metabolite, which will give it its anti-inflammatory effects.[18]

Reductive Bioactivation

Reductive activation is not very prevalent as compared to the oxidative processes, there are only a few reducing cells in the body. It is critical in the design of the anticancer drugs.[19]

Mitomycin C is an instance of an antineoplastic agent which is applied in the treatment of cancer-like diseases, lung cancers and bladder cancer. It has a quinone moiety which is reduced by the enzymes to hydroquinone. Such a change in the electronic state of the molecule allows production of highly reactive intermediates that can alkylate DNA thereby causing cytotoxic activity on the cancer cell.[20]

1.3 Mutual Prodrug

Mutual prodrugs are systems that consist of two active drugs that are covalently bonded together where one drug acts as a promoiety to the other. When administered the bond between the two is broken upon

physiological conditions releasing both the active drugs.[21]

This method can be conceptually likened to the rational drug design, in which drug compounds get altered to improve treatment effectiveness. Mutual prodrug design involves the selection of the components based on their complementary or synergistic mechanisms of action and delivery of two active agents at one site.[22]

The carrier drug can have a variety of applications. It may:

- Have the same therapeutic effects and result in synergies.
- Offer a different pharmacological action that is not available in parent drug.
- Make it possible to deliver to a target organ or tissue site-specifically.
- Aid in decreasing the undesirable effects of the parent drug.

Mutual prodrugs are of great help especially where combination therapy is a must since they are used to make sure that the two drugs are administered simultaneously in a controlled and effective form. It may lead to better therapeutic effect, enhanced drug delivery and decreasing toxicity.[23]

1.4 Polymeric Prodrug

Polymeric prodrug are systems where an active drug is covalently attached to a polymeric carrier, to create a macromolecular conjugate. Systems typically have been made to be biocompatible that is, they are non-toxic, non-immunogenic and safe therapeutically.[24]

The development of polymer-drug conjugates varies on a number of factors, such as chemical structure, molecular weight, steric effects and reactivity of the drug and the polymer. To be successfully conjugated, both of the components should have an appropriate functional group like -COOH, -OH, -NH 2 or -SH. Nevertheless, the existence of several reactive groups may complicate the synthesis and should be under control.[25]

The polymer carriers can be either powered or non-powered and depending on the mode of choice, the drug release profile and the biological behaviors may vary. The medication may be coupled to the polymer backbone or with an intermediate (so-called spacer) group which may be significant in determining how quickly and at what point the drug dissolves through enzymatic or hydrolytic variations.[26]

FUNDAMENTAL PRINCIPLES OF PRODRUG DESIGN

1. Bioavailability Barriers and Prodrug Solutions:

It is crucial to comprehend what unique barriers restrict bioavailability to accomplish rational prodrug design. The route through which an orally dispensed drug is followed is based on dissolution in gastrointestinal fluids, absorption through intestinal epithelium, and through the portal circulation, and possible first-pass metabolism in the liver. All steps represent a different problem which can be solved by the strategies of prodrug.[27]

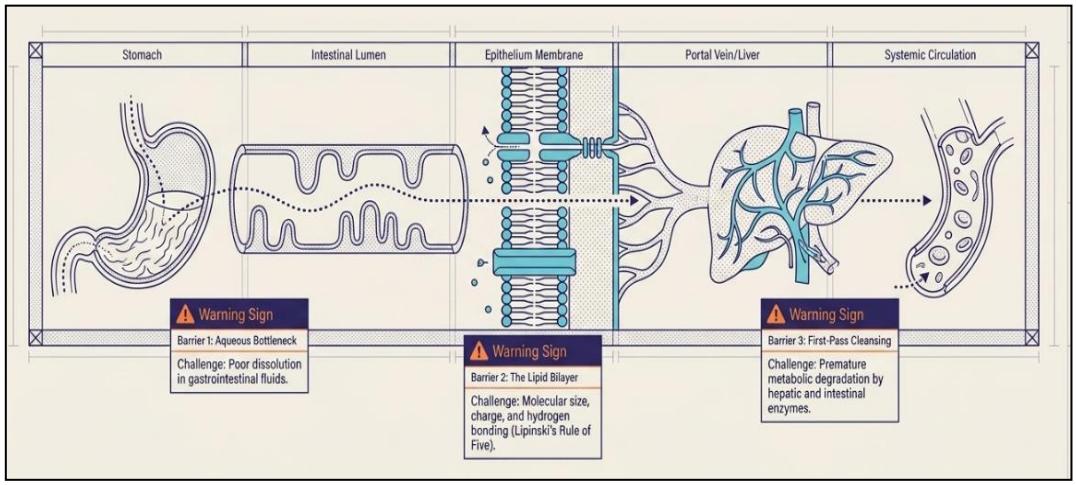

Figure 2. Major physiological barriers affecting oral drug bioavailability

The limited dissolution due to poor aqueous solubility of Class II and IV drugs can be a limiting factor to absorption because it forms an aqueous bottleneck. Introduction of ionizable groups, hydrophilic groups or structural groups can increase solubility via prodrug methods. Phosphate prodrug esters, such as allow greater water dissolution of the negatively charged phosphate atom in physiological pH and retain sufficient lipophilicity to enter membranes on dephosphorylation.[28]

Limitations in membrane permeability are based on the molecular attributes of size, charge and hydrogen bonding ability. A guideline of oral bioavailability is set by Lipinski (The Rule of Five), though in many essential cases of drug targets, molecules contravening such rules are necessary. Prodrug approaches can temporarily conceal polar functional groups, lower molecular weight by liberating promoieties or can use transporter-mediated uptake to circumvent permeability obstructions.[29]

Bioavailability of oxidable, conjugatable, or hydrolysable drugs can be significantly decreased by first-pass metabolism by intestinal mucosa and liver. Resistant prodrug designs, such as designs which resist premature metabolism or are saturation of a metabolic route of action, can enhance the proportion of drug in the systemic circulation. Also, prodrugs which can be activated by particular target tissue-enriched enzymes can avoid hepatic metabolism and specifically deliver to tissues.[30]

2. Chemical Strategies and Linkage Chemistry:

The promoiety-drug conjugation is another important design factor that defines stability, activation kinetic and bioavailability amplification. Ester bonds are the most prevalent since they can be synthesized and are hydrolyzed with certainty by widespread esterases. The stability of esters, however, can be significantly changed depending on steric and electronic factors and the activation rate can be tuned by several fold between minutes to hours.[31]

Substitutions with prodrugs have differing stability profiles and activation mechanisms, i.e., carbamate and carbonate prodrugs. Simple ester In comparison to simple derivatives, carbamate linkages tend to be more stable, yet susceptible to enzymatic degradation. Phenolic drugs have been successfully used with carbonate prodrugs, which offer increased stability in acidic environments, as well as give esterases and carbonic anhydrases an easy way in.[32]

Phosphate ester prodrugs are also a significant type especially with hydroxyl groups in the drugs. The phosphate group offers significant improvement in solubility but can be readily degraded by the intestinal-expressed alkaline phosphatases. An example of this approach is the phosphate ester prodrug of the HIV protease inhibitor amprenavir, called fosamprenavir, which exhibits better the bioavailability of the parent drug despite permeability similarity by 1.5-folds.[33]

Such complex chemical architectures as self-immolative linkers provide multi-step activation cascades. These systems include a spacer group between the drug and promoiety that spontaneously cleaves after the initial cleavage by an enzyme to release the parent drug by a cyclization or elimination reaction. This method has proven useful especially when it is chemically difficult to directly label the drug with the promoiety or controlled release kinetics are needed.[34]

3. Activation Mechanisms:

Activation Prodrug activation may be enzymatic or non-enzymatic, with each having its own benefits to the particular use. Tissue-targeted drug delivery may use enzymatic activation in the selectivity of enzyme expression patterns. Activating enzymes are common in the form of esterases, phosphatases, peptidases, and oxidoreductases and have distinct substrate specificities as well as tissue distribution.[35]

The most commonly used activating enzymes are carboxylesterases, which are highly expressed in liver and intestinal mucosa. Carboxylesterase 1 (hCE1) and carboxylesterase 2 (hCE2) have different substrate selectivity, as well as different expression patterns in tissues, and thus can be used to design prodrugs with selective activation profiles. Knowledge about speciation of carboxylesterase in expression and activity is important to overcome interdisciplinarity of preclinical data to clinical practice.[36]

The enzymes of cytochrome P450 can be utilized in the drug clearance and further metabolism but can be used to help activate prodrug by oxidation processes.

This method is especially pertinent when it comes to the tissue-specific delivery because various P450 isoforms do not demonstrate the same expression patterns. Prodrugs activated by CYP3A4 such as the above can be preferentially activated in the intestinal mucosa and liver, where this enzyme is strongly expressed.[37]

In non-enzymatic activations, pH-dependent hydrolysis, endogenous reducing agents like glutathione, and photochemical cleavages are the methods of activation. pH-sensitive prodrugs are drugs that take advantage of variations in pH between different biological compartments to allow the drug to be delivered directly to the target. As an illustration, the Schiff base linkages in the body remain intact at neutral pH and readily dissolve in acid to enable the drug release in the stomach or acidic tumor micro-systems.[38]

CARRIER-TARGETED PRODRUG APPROACHES

1. Nutrient Transporter-Targeted Prodrugs:

The exploitation of endogenous nutrient transporters is one of the most effective methods of increasing oral bioavailability. The small intestines have many amino acids, peptides, vitamins, organic nucleoside and organic ions expressed transporters that allow the efficient intake of essential nutrients. Imitation of these natural substrates as prodrugs will significantly enhance the absorption of poorly permeable drugs.[39]

Prodrug Amino acid transporter has been especially successful. Amino acid transporter systems are represented by ATB0,+ and LAT1 that transports various types of amino acids with different efficiency. The conjugation of drugs to amino acids like valine, leucine or phenylalanine can gain recognition by these transporters and significantly increase cellular uptake. An example of this strategy is valacyclovir, the valine prodrug of acyclovir, which has 3-5 fold greater bioavailability than acyclovir because of its effective absorption by the peptide transporter PEPT1.[40]

The applicant product of SLC15A1 mimics the peptide transporter PEPT1 (SLC15A1), which is expressed largely in the apical membrane of intestinal enterocytes and takes di- and tripeptide as substrates. This transporter has been widely used in the design of prodrugs and there have been many successful cases in this category including prodrugs of 2-Lactam antibiotics that resemble dipeptide structures. PEPT1 recognition has the important structural conditions of having a free carboxyl group and amino group in the alpha position and proper distance between the functional groups.[41]

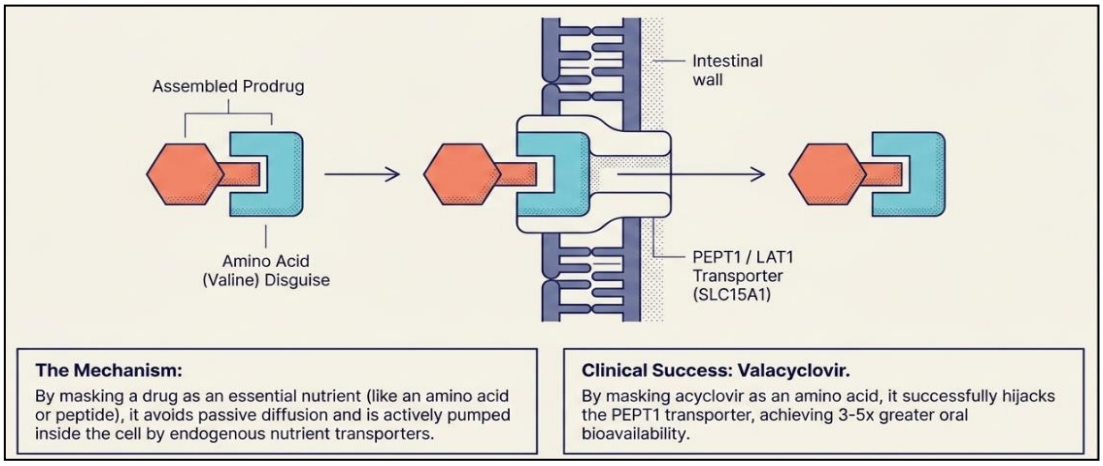

Figure 3. Transporter-mediated absorption of prodrugs

Another interesting target, however, to prodrug design can be monocarboxylases transporters (MCTs), especially when the drug to be conjugated is a short chain fatty acid drug. MCT1, which is found in intestinal epithelium, brain endothelium among other tissues, carries lactate, pyruvate, and other monocarboxylates. This transporter can be utilized by the use of enester prodrug conjugates to propionic or butyric acid and facilitate absorption and (probably) the delivery into the brain.[42]

2. Vitamin and Nucleoside Transporter-Mediated Delivery:

Vitamin transporters are an excellent transporter system that can be used to deliver prodrug. Folates are taken into cells by the proton-coupled folate transporter (PCFT) and reduced folate carrier (RFC) and biotin, pantothenic acid, and lipoic acid are taken into cells by sodium-dependent multivitamin transporter (SMVT). Drug conjugation to these vitamin moieties can be used to improve intestinal drug absorption and to specifically transport drugs to tissues that have high expression in vitamin transporters.[43]

Another route in regards to transporter-targeted prodrug delivery is through nucleoside transporters usually concentrative (CNTs) and equilibrative (ENTs) nucleoside transporters. These transporters have a general substrate specificity to both purine and pyrimidine nucleosides and, consequently, allow the design of nucleoside-drug conjugates that are likely to have higher levels of cellular uptake. This method is especially applicable to antiviral agents as well as anticancer agents which are acting on intracellular mechanisms.[44]

Capecitabine is a successful non-invasive illustration of bi-step activation of prodrug therapies that uses tumor-selective expression as well as absorption. After the oral administration, the capecitabine is broken down by different enzymes into 5-fluorouracil, and the last stage of activation is done by thymidine phosphorylase that is expressed more in tumor tissue than normal tissue. This design offers improved bioavailability, as well as tumor-selective delivery of drug.[45]

PERMEABILITY-ENHANCED PRODRUG STRATEGIES

1. Lipophilic Prodrugs:

The augmented lipophilicity by means of prodrug development is a traditional yet extremely topical method of raising membrane permeability. Simple fatty acid or alcohol esterification can radically raise lipophilicity to allow passive lipid membrane diffusion. An ideal lipophilicity should be that which takes into consideration, both, the membrane permeation and the solubility in the intestinal fluids.[46]

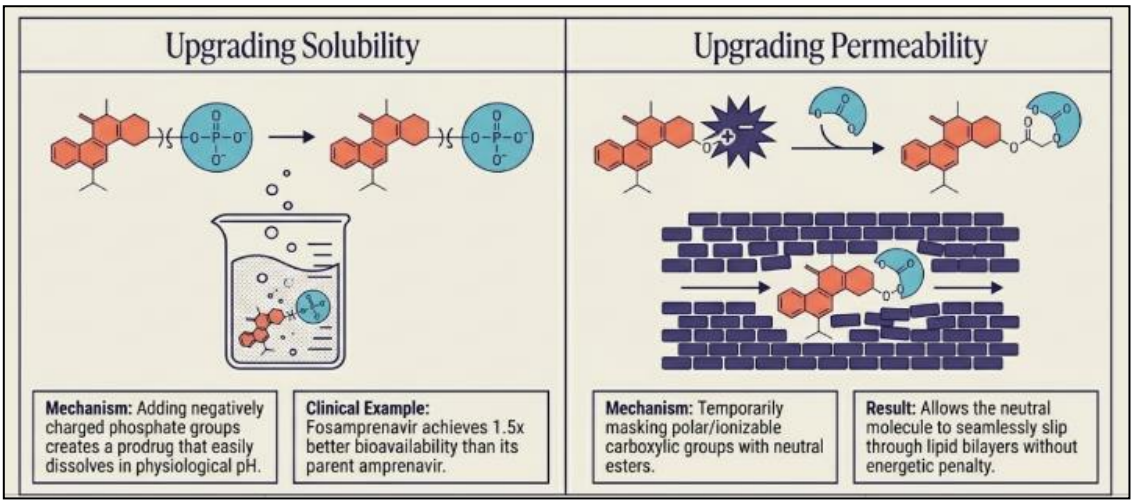

Figure 4. Prodrug strategies to enhance drug solubility and membrane permeability

An extension of this method is the concept of the use of long-chain fatty acids or phospholipids as promoieties, which results in the concept of lipid-drug conjugates. With these conjugates, they can form micelles, or can react with lipid transporting systems and may gain entry into the body via lymphatic routes bypassing the first-pass metabolism of the liver. Lymphatic absorption can be beneficial especially to drugs that are highly metabolized in the liver or drugs whose action is required in the lymphoid tissue.[47]

Prodrug structure Cyclic prodrug structures would allow them to be more permeable but retain enough aqueous solubility to dissolve. Cyclization causes a decrease in the amount of hydrogen bond acceptors and donors available to interact with aqueous chemistry and leads to higher membrane permeability, and such an effect may be achieved with large lipophilic substituents which are not required. The use of oxazolidinone and lactone prodrug

presents this strategy that exhibits better permeability and acceptable solubility properties.[48]

2. Masking Charged Groups:

Ionizable functional groups provide an advantage of solubility in aqueous solution, but can cause extreme depermeabilization of membranes since the cost of transfer of charged species across lipid bilayers is an energetic penalty. Prodrug measures allowing charged groups to be masked in the process of absorption allow the compounds to enter across membranes in neutral form and then restore the active charged species across the cell.[49]

Esters can be used to mask carboxylic groups found in most drugs such as NSAIDs, and antiviral agents. The resulting neutral ester is more permeable and further hydrolysis by intracellular or plasma esterases releases the active form of carboxylates. Tuning of both lipophilicity and activation kinetics can be done by proper choice of the ester substituents.[50]

Amino functional groups in most pharmaceuticals are maskable by means of cognition of carbamate, amide or Mannich base prodrugs. These techniques decrease basicity and hydrogen binding ability and promote membrane permeation. Tertiary amine prodrugs need to strike a balance between increase in permeability and have adequate stability to endure intestinal transit period and the activation kinetics to ensure the drug release occurs at the right time.[51]

Phosphate and sulfate functionalities, even though providing very good water solubility, seriously impair membrane permeation. This is the example of bisphosphonate drugs that are used to treat osteoporosis and exhibit dismal oral bioavailability (usually less than 1 percent). Although classical ester prodrug versions of phosphates are too unstable, other designs phosphoramidate and other novel phosphate prodrug designs have been reported to be useful in selective activation by enzymes.[52]

METABOLIC STABILITY ENHANCEMENT

1. Bypassing First-Pass Metabolism:

Hepatic first-pass metabolism is an important bioavailability limitation to many drugs. This challenge may be countered using prodrug strategies in a number of ways: saturation of metabolic pathways with the prodrug as the parent drug is produced at a regulated rate, prodrug resistance to the metabolic pathway in question and an alternative route to absorption avoiding hepatic metabolism to a degree.[53]

A beta-blocker, propranol, has very high hepatic extraction and hence oral bioavailability is about 30 to 35%. Prodrug methods have pursued several mechanisms of increasing bioavailability such as structures which resist cytochrome P450 hydrolysis and yet will be susceptible to esterase-based activation in systemic circulation upon clearance via the liver.[54]

There is another pathway called lymphatic absorption which can be used to reduce first-pass hepatic metabolism. The lipophilic prodrugs, especially those containing fatty acid compounds, have the ability of being transported in chylomicrons and taken into the systemic circulation via thoracic duct instead of the portal veins. It is especially useful with highly lipophilic (log P > 5) and first pass metabolized drugs.[55]

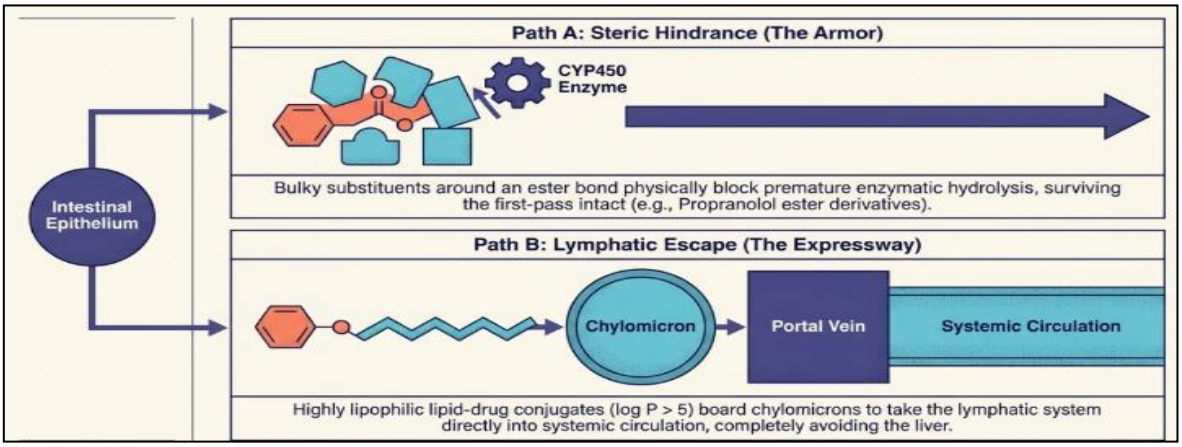

Figure 5. Prodrug strategies to bypass hepatic first-pass metabolism

2. Metabolically Stable Prodrug Designs:

Enzyme selectivity very much needs attention in designing prodrugs that can resist premature metabolism and at the same time be activated adequately upon reaching the target site. Knowledge of the precise metabolic routes involving a drug allows implementation of prodrugs to shun the relevant routes. In drugs where the active chemical moiety is metabolized by the P450 cytochrome enzymes, oxidative metabolism can be inhibited by masking metabolically labile sites with promoiety group.[56]

One method of controlling the activation kinetics and metabolic stability is sterically hindered ester. Large substituents around the ester bond can retard enzymatic hydrolysis and therefore the prodrug can pass intestines and hepatic first-pass and still be productively activated in plasma or target tissues. The method involves a tight control of stabilized and activation kinetic in order to obtain good bioreactivity.[57]

The use of two-step activation in the form of a double prodrug or pro-prodrug is associated with sequential activation steps, where primary conversion to a stable intermediate will precede the additional metabolism to cause the release of the active drug. The method offers the chance to have accurate control over the kinetics and topography of activation, however, this is at the expense of complexity and regulation in the chemical.[58]

SITE-SPECIFIC AND STIMULI-RESPONSIVE PRODRUGS

1. Disease-Activated Prodrugs:

The concept of disease-activated prodrugs deals with developing the molecules that are preferable activated in pathological tissue in terms of biochemical traits that may differentiate the pathologic tissue and the healthy tissue. This strategy facilitates improved bioavailability with improved absorption as well as site-specific drug delivery which improves efficacy with minimal side effects in the system.[59]

The prodrugs used to target tumors are active in response to biochemical characteristics of the tumor microenvironment such as hypoxia, acidic pH, increased enzyme expression and oxidative stress. Hypoxia-activated prodrugs (HAPs) are formed by the addition of nitroaromatic or quinone functional groups which are bioreductively activated under low oxygen, as seen in solid tumors. In these prodrugs, active transport is confined to tumors, namely, as a result of poor oxygenation of normal tissues and sufficient activity.[60]

Protease-activated prodrugs act on products of high expression of certain proteins by disease states. Cathepsins, and other proteases that are expressed include matrix metalloproteinases (MMPs) that are up regulated in cancer, inflammation, and other pathological states. Promoieties that are made in peptide form as substrates of these enzymes allow activation to be performed on a disease selective basis. This strategy has demonstrated specific possibilities to provide higher index therapeutic of cytotoxic agents.[61]

2. Organelle-Targeted Prodrugs:

Targeting drugs on subcellular levels with prodrug delivery methods have the potential to improve the efficacy of a treatment by making sure the drug concentration is concentrated in the particular subcellular organize that therapeutic targets are present. Mitochondrial targeting is an area that has attracted specific attention because of the central place played by mitochondrial dysfunction in diseases such as cancer, neurodegenerative diseases among other metabolic diseases.[62]

Triphenylphosphonium (TPP) cations take advantage of the negative mitochondrial membrane potential to acquire a high level of accumulation in mitochondria. Mitochondrial drug increases several hundred-fold compared to cytoplasm when conjugated with drugs or prodrugs to TPP moieties. This has been effectively used with antioxidants, anticancer agents as well as other therapeutics which focus on mitochondrial processes.[63]

Lysosomotropic prodrugs take advantage of the acidic pH of Lysosomes (pH 4.5-5.0) to release drugs into the organelles. Weakly basic promoieties are trapped in lysosomes by protonation and also ion entrapment and then the parent drug is released with help of acid. This method is more especially where the drug targets

a lysosomal enzyme or lysosomal dysfunction disease.[64]

EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

1. Computational Prodrug Design:

Prodrug design is also subjected to machine learning and artificial intelligence, which allows one to predict the physicochemical properties, metabolic stability and the biological activity. QSPR models trained on large statistical databanks can predict thousands of crucial parameters such as solubility, permeability and plasma stability based on molecular structure, accelerating prodrug optimization.[65]

The use of molecular dynamics simulations can give information about transporter- prodrug interactions, membrane permeation mechanisms and activation pathways. These computational methods have been shown to be able to find the best prodrugs even prior to synthesis saving huge amounts of man-hours and resources that would otherwise be used to develop a prodrug.[66]

2. Nanotechnology Integration:

The emerging nanoparticle- prodrug hybrid systems are systems that have merged the benefits of prodrug chemistry together with nanoparticle drug delivery. Nanoparticles can be used to release the prodrug at specific times, improve the stability of the prodrug, and target delivery. Self-assembling prodrug nanoparticles are free of excipients, and the drug release kinetics are highly controlled.[67]

Polymeric prodrug In nanostructures, polymeric prodrugs consist of several molecules of a drug that has been covalently conjugated with a polymer backbone and exhibit distinct pharmacokinetic properties. Such systems present long circulation time, high permeability and retention of tumors, and regulated release of drugs with respect to linker chemistry.[68]

3. Personalized Prodrug Therapy:

The variability in enzyme expression and activity in pharmacogenomic therapy offers the potential of individualized prodrug therapy. Esterase gene polymorphisms as well as cytochrome P450 enzymes and other activating enzymes can be of significant value in influencing a rate of prodrug activation and clinical outcome. The process of future prodrug development can be enhanced by genetic screening in order to target the best prodrug applications on patients depending on their genotype with respect to enzymes.[69]

CONCLUSION

Novel prodrug strategies have refined the strategy as not an easy tool to increase solubility to a complex platform to overcome various bioavailability obstacles and realize site-specific drug delivery. Recent developments on the understanding of absorption mechanisms, transporter biology, and biochemistry of diseases have led to rational development of prodrugs having drastically better therapeutic index.

Carrier-target prodrugs which utilize nutrient transporters are one of the most successful recent strategies, clinical examples of which have shown significant improvements in bioavailability. This can be done through integration of metabolic stability concerns with increase of the permeabilities so as to provide holistic solutions to extremely difficult bioavailability problems. The development of stimuli-responsive as well as disease-activated prodrug will deliver better pharmacokinetics and greater therapeutic selectivity.

Technology areas to be integrated in the future are incorporation of computational design tools, nanotechnological platforms and personalized medicine. Since research on the phenomenon of biological barriers and activation will only keep developing, prodrug strategies will be the one that will serve pharmaceutical scientists and help them in dealing with the ongoing challenge of bioavailability optimisation. The drug development success of prodrug strategies is confirmed all over time and provides continued innovation in this dynamic field.

REFERENCES

1. Rautio, J., Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and development. Nature Reviews Drug Discovery, 17(8), 559–587. https://doi.org/10.1038/nrd.2018.46

2. Dahan, A., & Hoffman, A. (2009). Prediction of solubility and permeability class membership: Provisional BCS classification of the world's top oral drugs. The AAPS Journal, 11(4), 740–746. https://doi.org/10.1208/s12248-009-9144-x
3. Ahire, E. D., Thackeray, S. J., Bhosale, R. R., Bhosale, S., Bairagi, V. A., & Kale, S. (2023). Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. Life, 13(5), Article 1099. https://doi.org/10.3390/life13051099
4. Brandsch, M. (2013). Drug transport via the intestinal peptide transporter PepT1. Current Opinion in Pharmacology, 13(6), 881–887. https://doi.org/10.1016/j.coph.2013.08.004
5. Xu, W., Jia, A., Lei, Z., Wang, J., Jiang, H., Wang, S., & Wang, Q. (2024). Stimuli-responsive prodrugs with self-immolative linker for improved cancer therapy. European Journal of Medicinal Chemistry, 279, Article 116928. https://doi.org/10.1016/j.ejmech.2024.116928
6. Umerska, A., & Paluch, K. J. (2020). Prodrugs for improved drug delivery: Lessons learned from recently developed and marketed products. Pharmaceutics, 12(11), Article 1071. https://doi.org/10.3390/pharmaceutics12111071
7. Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. (2008). Prodrugs: Design and clinical applications. Nature Reviews Drug Discovery, 7(3), 255–270. https://doi.org/10.1038/nrd2468
8. Stella, V. J., & Nti-Addae, K. W. (2007). Prodrug strategies to overcome poor water solubility. Advanced Drug Delivery Reviews, 59(7), 677–694. https://doi.org/10.1016/j.addr.2007.05.013
9. Ettmayer, P., Amidon, G. L., Clement, B., & Testa, B. (2004). Lessons learned from marketed and investigational prodrugs. Journal of Medicinal Chemistry, 47(10), 2393–2404. https://doi.org/10.1021/jm0303812
10. Mandell, A. I., Stentz, F., & Kitabchi, A. E. (1978). Dipivalyl epinephrine: A new pro-drug in the treatment of glaucoma. Ophthalmology, 85(3), 268–275. https://doi.org/10.1016/S0161-6420(78)35696-4
11. Bundgaard, H., & Johansen, M. (1980). Pilocarpine prodrugs II. Synthesis, stability, bioconversion, and physicochemical properties of sequentially labile pilocarpine acid diesters. Journal of Pharmaceutical Sciences, 69(1), 44–50. https://doi.org/10.1002/jps.2600690111
12. Mehta, P. P., Chabukswar, A. R., & Jagdale, S. C. (2019). Carriers for prodrug synthesis: A review. International Journal of Pharmaceutical Sciences and Drug Research, 11(3), 83–92. https://www.ijpsonline.com/articles/carriers-for-prodrug-synthesis-a-review-3634.html
13. Mahato, R., Tai, W., & Cheng, K. (2011). Prodrugs for improving tumor targetability and efficiency. Advanced Drug Delivery Reviews, 63(8), 659–670. https://doi.org/10.1016/j.addr.2011.02.002
14. Barar, J., & Omidi, Y. (2014). Dysregulated pH in tumor microenvironment checkmates cancer therapy. BioImpacts, 3(4), 175–187. https://doi.org/10.5681/bi.2013.036
15. Kokil, G. R., & Rewatkar, P. V. (2010). Bioprecursor prodrugs: Molecular modification of the active principle. Mini Reviews in Medicinal Chemistry, 10(14), 1316–1330. https://doi.org/10.2174/138955710793564179
16. Huttunen, K. M., Raunio, H., & Rautio, J. (2011). Prodrugs — from serendipity to rational design. Pharmacological Reviews, 63(3), 750–771. https://doi.org/10.1124/pr.110.003459
17. Huttunen, K. M., Raunio, H., & Rautio, J. (2011). Prodrugs — from serendipity to rational design. Pharmacological Reviews, 63(3), 750–771. https://doi.org/10.1124/pr.110.003459
18. Patel, J. B., Wahawasan, G., Bhimani, B., Patel, B., Gajjar, V., & Bhatt, P. A. (2009). A predominant role of CYP1A2 for the metabolism of nabumetone to the active metabolite, 6-methoxy-2-naphthylacetic acid, in human liver microsomes. Drug Metabolism and Disposition, 37(5), 1019–1025. https://doi.org/10.1124/dmd.108.025593
19. Kokil, G. R., & Rewatkar, P. V. (2010). Bioprecursor prodrugs: Molecular modification of the active principle. Mini Reviews in Medicinal Chemistry, 10(14), 1316–1330. https://doi.org/10.2174/138955710793564179
20. Tomasz, M., & Palom, Y. (1997). The mitomycin bioreductive antitumor agents: Cross-linking and alkylation of DNA as the molecular basis of their activity. Pharmacology & Therapeutics, 76(1–3), 73–87. https://doi.org/10.1016/S0163-7258(97)00088-0

21. Karaman, R., & Dajani, R. (2023). Mutual prodrugs — codrugs. Current Medicinal Chemistry, 30(38), 4283–4339. https://doi.org/10.2174/0929867330666221209102650
22. Cavalli, A., Bolognesi, M. L., Minarini, A., Rosini, M., Tumiatti, V., Recanatini, M., & Melchiorre, C. (2008). Multi-target-directed ligands to combat neurodegenerative diseases. Journal of Medicinal Chemistry, 51(3), 347–372. https://doi.org/10.1021/jm7009364
23. Intagliata, S., Salerno, L., Ciaffaglione, V., Leonardi, C., Fallica, A. N., Caraci, F., Ronsisvalle, S., Pittala, V., Romeo, G., & Modica, M. N. (2019). Mutual prodrugs of 5-fluorouracil: From a classic chemotherapeutic agent to novel potential anticancer drugs. ChemMedChem, 14(17), 1546–1564. https://doi.org/10.1002/cmdc.201900325
24. Hu, Q., Katti, P. S., & Gu, Z. (2015). Polymer-based prodrugs: Improving tumor targeting and the solubility of small molecule drugs in cancer therapy. Molecules, 20(12), 19804–19830. https://doi.org/10.3390/molecules201219804
25. Matera, C., & Dallanoce, C. (2020). Polymer–drug conjugates: Recent advances and future perspectives. Drug Discovery Today, 25(9), 1718–1734. https://doi.org/10.1016/j.drudis.2020.07.008
26. Kopecek, J., & Kopeckova, P. (2010). HPMA copolymers: Origins, early developments, present, and future. Advanced Drug Delivery Reviews, 62(2), 122–149. https://doi.org/10.1016/j.addr.2009.10.004
27. Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and development. Nature Reviews Drug Discovery, 17(8), 559–587. https://doi.org/10.1038/nrd.2018.46
28. Liederer, B. M., & Borchardt, R. T. (2006). Enzymes involved in the bioconversion of ester-based prodrugs. Journal of Pharmaceutical Sciences, 95(6), 1177–1195. https://doi.org/10.1002/jps.20542
29. Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 46(1–3), 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0
30. Umerska, A., & Paluch, K. J. (2020). Prodrugs for improved drug delivery: Lessons learned from recently developed and marketed products. Pharmaceutics, 12(11), Article 1071. https://doi.org/10.3390/pharmaceutics12111071
31. Takahashi, M., Hirota, I., Nakano, T., Kotani, T., Takani, D., Shiratori, K., Choi, Y., Haba, M., & Hosokawa, M. (2021). Effects of steric hindrance and electron density of ester prodrugs on controlling the metabolic activation by human carboxylesterase. Journal of Pharmaceutical and Biomedical Analysis, 200, Article 114067. https://doi.org/10.1016/j.jpba.2021.114067
32. Mayer, A., Glombik, H., & Quirmbach, M. (2015). Organic carbamates in drug design and medicinal chemistry. Journal of Medicinal Chemistry, 58(3), 1067–1088. https://doi.org/10.1021/jm501371s
33. Wire, M. B., Shelton, M. J., & Studenberg, S. (2006). Fosamprenavir: Clinical pharmacokinetics and drug interactions of the amprenavir prodrug. Clinical Pharmacokinetics, 45(2), 137–168. https://doi.org/10.2165/00003088-200645020-00002
34. Dal Corso, A., Pignataro, L., Belvisi, L., & Gennari, C. (2019). Innovative linker strategies for tumor-targeted drug conjugates. Chemistry — A European Journal, 25(52), 14040–14060. https://doi.org/10.1002/chem.201903127
35. Rautio, J., Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and development. Nature Reviews Drug Discovery, 17(8), 559–587. https://doi.org/10.1038/nrd.2018.46
36. Di, L. (2019). The impact of carboxylesterases in drug metabolism and pharmacokinetics. Current Drug Metabolism, 20(2), 91–102. https://doi.org/10.2174/1389200219666180821094502
37. Thummel, K. E., & Wilkinson, G. R. (1998). In vitro and in vivo drug interactions involving human CYP3A. Annual Review of Pharmacology and Toxicology, 38, 389–430. https://doi.org/10.1146/annurev.pharmtox.38.1.389

38. Zhai, Y., Zhou, X., Zhang, Z., Zhang, L., Wang, D., Wang, X., & Sun, W. (2018). Design, synthesis, and characterization of Schiff base bond-linked pH-responsive doxorubicin prodrug based on functionalized mPEG-PCL for targeted cancer therapy. Polymers, 10(10), Article 1127. https://doi.org/10.3390/polym10101127
39. Liang, E., Chessic, K., & Yazdanian, M. (2021). Intestinal solute carriers: An overview of trends and strategies for improving oral drug absorption. Frontiers in Pharmacology, 12, Article 618411. https://doi.org/10.3389/fphar.2021.618411
40. Hu, M., Subramanian, P., Mosberg, H. I., & Amidon, G. L. (1989). Use of the peptide carrier system to improve the intestinal absorption of L-alpha-methyldopa: carrier kinetics, intestinal permeabilities, and in vitro hydrolysis of dipeptidyl derivatives of L-alpha-methyldopa. Pharmaceutical Research, 6(1), 66–70. https://doi.org/10.1023/A:1015913608248
41. Minhas, G. S., & Newstead, S. (2019). Structural basis for prodrug recognition by the SLC15 family of proton-coupled peptide transporters. Proceedings of the National Academy of Sciences of the United States of America, 116(3), 804–809. https://doi.org/10.1073/pnas.1813715116
42. Vijay, N., & Morris, M. E. (2014). Role of monocarboxylate transporters in drug delivery to the brain. Current Pharmaceutical Design, 20(10), 1487–1498. https://doi.org/10.2174/13816128113199990462
43. Matherly, L. H., Wilson, M. R., & Hou, Z. (2014). The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: Biology and role in antifolate chemotherapy of cancer. Drug Metabolism and Disposition, 42(4), 632–649. https://doi.org/10.1124/dmd.113.056176
44. Baldwin, S. A., Beal, P. R., Yao, S. Y. M., King, A. E., Cass, C. E., & Young, J. D. (2004). The equilibrative nucleoside transporter family, SLC29. Pflügers Archiv — European Journal of Physiology, 447(5), 735–743. https://doi.org/10.1007/s00424-003-1103-2
45. Walko, C. M., & Lindley, C. (2005). Capecitabine: A review. Clinical Therapeutics, 27(1), 23–44. https://doi.org/10.1016/j.clinthera.2005.01.005
46. Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. (2008). Prodrugs: Design and clinical applications. Nature Reviews Drug Discovery, 7(3), 255–270. https://doi.org/10.1038/nrd2468
47. Fattahi, N., Shahbazi, M.-A., Maleki, A., Hamidi, M., Ramazani, A., & Santos, H. A. (2021). Emerging insights on drug delivery by fatty acid mediated synthesis of lipophilic prodrugs as novel nanomedicines. Journal of Controlled Release, 326, 556–598. https://doi.org/10.1016/j.jconrel.2020.07.012
48. Barlow, N., Chalmers, D. K., Williams-Noonan, B. J., Thompson, P. E., & Norton, R. S. (2020). Improving membrane permeation in the beyond rule-of-five space by using prodrugs to mask hydrogen bond donors. ACS Chemical Biology, 15(8), 2070–2078. https://doi.org/10.1021/acschembio.0c00218
49. Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. (2008). Prodrugs: Design and clinical applications. Nature Reviews Drug Discovery, 7(3), 255–270. https://doi.org/10.1038/nrd2468
50. Laizure, S. C., Herring, V., Hu, Z., Witbrodt, K., & Parker, R. B. (2013). The role of human carboxylesterases in drug metabolism: Have we overlooked their importance? Pharmacotherapy, 33(2), 210–222. https://doi.org/10.1002/phar.1194
51. Simplício, A. L., Clancy, J. M., & Gilmer, J. F. (2008). Prodrugs for amines. Molecules, 13(3), 519–547. https://doi.org/10.3390/molecules13030519
52. Wiemer, A. J., & Wiemer, D. F. (2014). Prodrugs of phosphonates and phosphates: Crossing the membrane barrier. Topics in Current Chemistry, 360, 115–160. https://doi.org/10.1007/128_2014_561
53. Pond, S. M., & Tozer, T. N. (1984). First-pass elimination: Basic concepts and clinical consequences. Clinical Pharmacokinetics, 9(1), 1–25. https://doi.org/10.2165/00003088-198409010-00001
54. Schneck, D. W., & Vary, J. E. (1984). Mechanisms by which hydralazine increases propranolol bioavailability. Clinical Pharmacology & Therapeutics, 35(4), 447–453. https://doi.org/10.1038/clpt.1984.57
55. Trevaskis, N. L., Kaminskas, L. M., & Porter, C. J. H. (2015). From sewer to saviour — targeting

the lymphatic system to promote drug exposure and activity. Nature Reviews Drug Discovery, 14(11), 781–803. https://doi.org/10.1038/nrd4608

56. Markovic, M., Ben-Shabat, S., & Dahan, A. (2020). Computational simulations to guide enzyme-mediated prodrug activation. International Journal of Molecular Sciences, 21(10), Article 3621. https://doi.org/10.3390/ijms21103621
57. Takahashi, T., Mabuchi, M., Hirota, K., Itagaki, F., Hamao, T., & Homma, M. (2021). Effects of steric hindrance and electron density of ester prodrugs on controlling the metabolic activation by human carboxylesterase. Drug Metabolism and Pharmacokinetics, 36, Article 100366. https://doi.org/10.1016/j.dmpk.2020.100366
58. Huttunen, K. M., Raunio, H., & Rautio, J. (2011). Prodrugs — from serendipity to rational design. Pharmacological Reviews, 63(3), 750–771. https://doi.org/10.1124/pr.110.003459
59. Rautio, J., Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and therapy. Nature Reviews Drug Discovery, 17(8), 559–587. https://doi.org/10.1038/nrd.2018.46
60. Fu, S., Yang, R., Ren, J., Liu, J., Zhang, L., Xu, Z., Kang, Y., & Xue, P. (2021). Targeting hypoxia: Hypoxia-activated prodrugs in cancer therapy. Frontiers in Oncology, 11, Article 700407. https://doi.org/10.3389/fonc.2021.700407
61. Poreba, M. (2020). Protease-activated prodrugs: Strategies, challenges, and future directions. FEBS Journal, 287(10), 1936–1969. https://doi.org/10.1111/febs.15227
62. Cheng, X., Feng, D., Lv, J., Cui, X., Wang, Y., Wang, Q., & Zhang, L. (2023). Application prospects of triphenylphosphine-based mitochondria-targeted cancer therapy. Cancers, 15(3), Article 666. https://doi.org/10.3390/cancers15030666
63. Murphy, M. P. (2008). Targeting lipophilic cations to mitochondria. Biochimica et Biophysica Acta — Bioenergetics, 1777(7–8), 1028–1031. https://doi.org/10.1016/j.bbabio.2008.03.029
64. Hu, Q., Sun, W., Wang, C., & Gu, Z. (2016). Recent advances of cocktail chemotherapy by combination drug delivery systems. Advanced Drug Delivery Reviews, 98, 19–34. https://doi.org/10.1016/j.addr.2015.10.022
65. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7, Article 42717. https://doi.org/10.1038/srep42717
66. Markovic, M., Ben-Shabat, S., & Dahan, A. (2020). Computational simulations to guide enzyme-mediated prodrug activation. International Journal of Molecular Sciences, 21(10), Article 3621. https://doi.org/10.3390/ijms21103621
67. Maksimenko, A., Dosio, F., Mougin, J., Ferrero, A., Wack, S., Reddy, L. H., Weiswald, L.-B., Габриель, C., Dhommée, C., Puisieux, A., Paci, A., Couvreur, P., & Stella, B. (2023). Self-assembled lipid–prodrug nanoparticles. Nature Reviews Bioengineering, 1, 543–559. https://doi.org/10.1038/s44222-023-00082-0
68. Hruby, M., Konak, C., & Ulbrich, K. (2005). Polymeric micellar pH-sensitive drug delivery system for doxorubicin. Journal of Controlled Release, 103(1), 137–148. https://doi.org/10.1016/j.jconrel.2004.11.016
69. Zanger, U. M., & Schwab, M. (2013). Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics, 138(1), 103–141. https://doi.org/10.1016/j.pharmthera.2012.12.007

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