

AN OVERVIEW OF FUTURE PROSPECTIVE IN PRODRUGS DEVELOPMENT

Abstract

Prodrugs, which are chemically altered substances that go through biotransformation to release the active ingredient, offer better medication stability and specialised delivery. Prodrug creation has had a major influence on contemporary drug discovery throughout history, from the isolation of active molecules during the Scientific Revolution through the use of traditional herbal treatments. Structure-activity correlations, optimization approaches, and design principles all take strategic changes into account. Enzymatic, pharmacological, and pH-dependent activation mechanisms allow for controlled drug release and therapeutic activity at a specific spot. Prodrug carriers and nanoparticle-based approaches have the potential to transport drugs to particular areas of the body, opening the door to personalised medicine and disease-specific therapies. Successful case studies highlight transformational medicines for a range of disorders despite obstacles in toxicity, bioavailability, and stability. Through clinical trials, regulatory inspection, and post-marketing monitoring, the clinical development process is rigorously evaluated. Looking ahead, prodrug uses in gene therapy and biologics, tailored therapeutics, and developing trends provide interesting opportunities for pharmacological interventions. Prodrugs' full potential will be unlocked through embracing innovation and solving problems, transforming medication delivery and patient care.

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I. INTRODUCTION

Prodrugs are chemically altered forms of pharmacological substances that require a metabolic conversion to release the active ingredient after delivery. They have been routinely employed to get around different problems with medication delivery and boost therapeutic effectiveness. The goal of this chapter is to give a general review of prodrug development and its uses.

A well-known example of a prodrug that has undergone substantial pharmacological development throughout time is amphetamine. Due of the possibility of misuse, it was once freely available but is now very limited. For it to be used clinically, benefit and risk must be balanced [1].

Lisdexamfetamine (LDX) is an amphetamine prodrug approved for the management of attention deficit hyperactivity disorder (ADHD). Its distinctive pharmacokinetic/pharmacodynamic profile contributes to sustained efficacy as a treatment for ADHD while reducing its potential for recreational abuse [2].

Dopamine replacement therapy using levodopa (LD) is commonly used in Parkinson's disease (PD). However, LD faces challenges such as poor blood-brain barrier penetration and decreased response over time. Prodrugs have been developed to enhance LD's stability, blood-brain barrier penetration, and pharmacokinetics. These include ester prodrugs for intranasal delivery and amide/dimeric amide prodrugs with enhanced blood-brain barrier penetration and better pharmacokinetics [3].

Capecitabine is an oral prodrug converted into fluorouracil (FU) in tumor tissue. It was developed to improve tolerability and intratumor drug concentrations compared to parenteral FU administration. Capecitabine has shown efficacy with acceptable tolerability in various cancers, including breast and colorectal cancer [4].

Gemcitabine is a nucleoside analog used as an anticancer drug for various conditions. However, enzymatic deamination, fast systemic clearance, and chemoresistance limit its efficacy. Prodrug strategies have been explored to enhance gemcitabine's pharmacokinetic properties, safety, and targeted delivery [5].

Lisdexamfetamedimesylate (LDX) is the first long-acting prodrug stimulant approved for ADHD treatment. Safety evaluations of LDX showed that it has a similar profile to other stimulants used for ADHD treatment [6]. In adults, LDX has a lower potential for abuse than immediate-release dexamphetamine [6].

ProTide technology is a phosphate prodrug method designed to deliver nucleoside monophosphates intracellularly. It has been successful in transforming the drug discovery of antiviral and anticancer nucleoside analogs by improving therapeutic efficiency and reducing side effects [7].

The use of antibody prodrugs shows promise in widening the therapeutic window of potent biological therapies for cancer by improving tumor specificity. Probody therapeutics are antibody-based prodrugs that have demonstrated potent antitumor activity with improved safety profiles in preclinical studies and early clinical trials [8].

1. Purpose and Advantages of Prodrug Development: Prodrugs are derivatives of therapeutic agents designed to improve the pharmacokinetic profile of the drug [9]. They mask the pharmacological activity of the drug and are converted into active drugs within the body through bioconversion processes mediated by enzymes [9]. Prodrug development offers several advantages in drug delivery and therapy. One advantage is improved site-specific bioconversion achieved through enzyme prodrug therapy (EPT) [9]. EPT involves designing prodrugs that can be specifically activated by non-mammalian or low-abundance enzymes at target sites [9]. This approach allows for targeted drug release and reduces off-target effects. Self-immolative linkers have been developed to further enhance prodrug design for EPT, enabling controlled release mechanisms [9].

Another advantage is enhanced pharmacokinetics and drug delivery properties. Human serum albumin (HSA)-based therapeutics have attracted attention in anticancer agent development due to their versatile properties [10]. HSA-based systems can improve pharmacokinetics, extend circulation half-life, enhance efficacy, reduce toxicity, and enable tumor site-oriented therapeutics through enhanced penetration and retention effects [10].

Furthermore, prodrugs can be designed to respond to specific stimuli for controlled release at target sites. For example, a ROS-responsive simvastatin nano-prodrug was developed for atherosclerosis treatment [11]. This nanoprodrug released parent simvastatin in response to hydrogen peroxide present at atherosclerotic plaques, allowing targeted drug release with reduced off-target leakage [11].

Supramolecular prodrugs based on host-guest interactions offer another strategy for controlled drug release. These prodrugs form supramolecular complexes that can be triggered to release the active drug in a controlled manner [12]. This approach provides advantages such as ease of preparation, molecular-level protection, sensitive response to bio-stimuli, traceless release, and adaptability to different drugs [12].

Prodrug-based nanoparticle therapeutics have also emerged as promising drug delivery systems. These systems combine the advantages of prodrugs and nanoparticles, including high drug loading efficiency, low carrier-induced immunogenicity, tumor stimuli-responsive drug release, and combinational therapy [13].

Several prodrug-based nanoparticle formulations are currently in clinical development. In addition to these advantages, prodrugs can be designed for targeted cancer therapy by exploiting unique markers overexpressed by cancer cells. Antibody-drug conjugates (ADCs) are commonly used in targeted cancer therapy [14]. However, challenges such as limited uptake and poor pharmacokinetics need to be addressed. Combining prodrugs with nanotechnology or other approaches like aptamer-conjugated nanomaterials may offer more efficient strategies for targeted cancer therapy [14].

Overall, prodrug development offers several advantages in improving pharmacokinetic profiles of drugs and enabling targeted drug delivery. Strategies such as EPT, HSA-based therapeutics, stimulus-responsive systems, supramolecular interactions, and nanoparticle-based delivery systems show promise in enhancing the efficacy and

safety of therapeutic agents. Prodrug development offers significant potential for enhancing drug delivery, improving therapeutic efficacy, reducing toxicity or abuse potential, and overcoming challenges associated with specific drugs or diseases.

2. Factors Influencing Prodrug Design: To successfully develop a prodrug that is effective, a complex and highly nuanced process called prodrug design must be followed. The stability, activation, targeting potential, and overall therapeutic advantages of the prodrug are significantly influenced by these variables. The main elements that affect prodrug design are listed below:

- **Chemical Stability:** The chemical stability of the prodrug itself is one of the main factors to be taken into account while designing prodrugs. It should be sufficiently stable during production, storage, and transportation to ensure that it holds together until it reaches the intended location. When administered, the prodrug should have the ability to undergo biotransformation in order to release the active medication. It's critical to strike the correct balance between stimulation and stability. [15]
- **Bioreversibility:** Prodrugs need to be made such that the activation process may be reversed in order to effectively release the parent medication at the targeted site of action. This bioreversibility makes sure that the prodrug is quickly transformed back into the active medication after performing its purpose, enabling the body's natural clearance systems to efficiently discard it. [16]
- **Biocompatibility and Safety:** Prodrugs should not cause any adverse effects and should not include any inherent pharmacological activity that may cause them. The chemical alterations used during prodrug creation shouldn't result in any negative side effects or disrupt regular physiological functions. [17]
- **Targeting Capabilities:** Achieving site-specific drug delivery is a critical factor in prodrug design. By attaching targeting moieties or carriers to the prodrug, it becomes possible to direct the drug to specific tissues or cells, maximizing its therapeutic efficacy while minimizing systemic exposure and off-target effects. [18]
- **Route of Administration:** When designing prodrugs, it is important to take specific issues associated with each route of drug administration, such as oral, intravenous, topical, and intramuscular, into account. For instance, prodrugs intended for oral administration should be resistant to breakdown in the gastrointestinal system, whereas those meant for topical application should be able to adequately permeate the skin. [19]
- **Expression of Enzymes and Transporters:** The selection of the enzymes or transporters in charge of prodrug activation is essential. Prodrug design may be influenced by knowledge of the location and expression levels of these enzymes and transporters in target organs. Individual differences in these enzymes' availability and activity might affect a prodrug's effectiveness and a patient's reaction. [20]
- **Pharmacokinetic Properties:** The ADME (absorption, distribution, metabolism, and excretion) profiles of pharmaceuticals should be improved while creating prodrugs. Prodrugs can boost bioavailability, prolong drug half-life, and enhance therapeutic results by increasing these pharmacokinetic features.. [21]
- **Therapeutic Indication:** When designing a prodrug, it is important to consider the desired therapeutic indication. Customized prodrug designs are required to handle the particular problems associated with each indication since different illnesses or conditions may call for different strategies for drug delivery and activation.

- **Considerations Regarding Intellectual Property:** Prodrug development must prioritise protecting intellectual property (IP). Patent protection may be available for novel prodrug compositions that significantly outperform already available medications, giving them market exclusivity and financial benefits. [7]
- 3. Structure-Activity Relationships (SAR) and Prodrug Optimization:** Structure-activity relationships (SAR) study the connection between a molecule's three-dimensional structure and its biological activity. SAR is critical in determining the structural characteristics of the lead chemical that are necessary for its biological activity in the context of prodrug optimization. Researchers can change the prodrug's chemical structure to improve its pharmacokinetic and pharmacodynamic effects by studying the SAR.
 - 4. An Illustration of the Idea of SAR and Prodrug Optimization is Provided here:** Let's think about an imaginary lead molecule with strong anti-inflammatory properties but low oral bioavailability. The SAR analysis demonstrates that the lead compound's anti-inflammatory action is due to a particular functional group. This functional group does, however, also contribute to its low solubility.

Researchers can create a prodrug that preserves the crucial functional group necessary for activity while including other alterations to boost solubility in order to maximise the prodrug. They can add a hydrophilic moiety or a pro-moiety that can be broken down by enzymes or chemicals to release the active ingredient.

For instance, they could create a prodrug with an ester bond that the body can easily hydrolyze to release the active ingredient. By making this change, the prodrug becomes more soluble while retaining the crucial pharmacophore needed for anti-inflammatory efficacy.

Researchers can create a balance between stability and activation by modifying the prodrug based on SAR analysis, improving the prodrug's therapeutic advantages. The solubility of the modified prodrug may be increased, enabling better absorption and distribution and, eventually, enhancing therapeutic effectiveness.

The development of amtolmetinguacil is one successful instance of prodrug optimization. Tolmetin is an anti-inflammatory medication. AmtolmetinGuacil is a lipophilic prodrug of tolmetin. It was created to lessen gastrointestinal adverse effects and increase the drug's solubility.

The prodrug amtolmetinguacil was created by esterifying tolmetin with guaiacol, a lipophilic moiety, and it showed better solubility and increased oral bioavailability. Amtolmetinguacil is quickly hydrolyzed in the body after administration to liberate tolmetin, the active ingredient. Better distribution and absorption of the medicine were made possible by this prodrug design, which increased therapeutic effectiveness. [22]

II. PRODRUG ACTIVATION MECHANISM:

- 1. Enzymatic Prodrug Activation Mechanism:** Prodrug activation can be done by various enzymes, which includes from oxidoreductases like Cytochrome P450 to hydrolytic enzymes.

- **Cytochrome P450 (CYP450):** There is a proof that genetic polymorphisms of Cytochrome P450 enzymes makes various prodrugs for activation, which leads to safety and effectiveness of drugs. The Cytochrome enzymes such as CYP1A2, 2C19, 2B6, 2C9, 2C8, 2E1, 2D6, 3A5, 3A4 are involved in metabolism of drug and activates the prodrug. Mainly CYP3A4 are involved in metabolism and prodrug activation as it is rich in hepatic tissues. CYP2C9 is an CYP enzyme which is responsible for metabolism of almost 15% of drugs which is present in the market. Few Variants of the CYP2C9 involves in reduced enzymatic activity because of polymorphism, thereby it affects the clinical response of the drugs. To overcome this problem, structural variations in CYP2C9*2, *8,*3,*5,*13,*11 CYP2C9 variants are responsible for variable enzyme mediated activation of certain drugs.
- **Carboxylesterase:** Human carboxylesterase typically hydrolyzes prodrugs with ester linkages (hCE). Humans have two primary hCEs, hCE1 and hCE2. Because hCE1 has a shorter catalytic site, it can cleave smaller substrates, whereas hCE2 has a larger catalytic site. This enzyme's catalytic site is distinguished by serine, histidine, and glutamine. The carbonyl group of an ester prodrug is attacked by the hydroxyl group found in serine. In the process of creating prodrugs, MD and QM approaches are applied to provide optimal accommodation inside the catalytical sites of hCE1.
- **Phospholipase A2 (PLA2):** Phospholipase 2 is overexpressed in cancer and many inflammatory diseases (PL2). This enzyme assists in the phospholipid's sn bond's hydrolysis. Therefore, a medicine must be created in a method that will hydrolyze the phospholipid link and enable efficient drug delivery to the site of action. This led to the development of a PL prodrug that covalently binds to the sn2 site of PL and lowers the overexpression of PLA2. In order to measure the effectiveness of the planned PL prodrug, an MD simulation was created. According to the simulation's findings, the PL prodrug acts on an enzyme's active site's well-defined transition state geometry, which is characterised by interactions between the calcium atom from the PLA2 and the sn2 carbonyl oxygen. [23]
- **Cholinesterase:** Specific biomarkers, such as dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) and cholinesterase, are used to diagnose and monitor Alzheimer's disease (ChE). As a result, a new prodrug was created that targets these indicators. There is a carbonate connection between DYRK1A and ChE. Currently, only the oxidised version of the intended prodrug displays the strong inhibition of ChEs. A review employing molecular docking software found that the developed prodrug's ability to inhibit ChE might be explained by a pseudo irreversible mechanism and that the carbonate connection between the two biomarkers hides the drug's ability to inhibit DYRK1A [23].
- **Chemical Activation of Prodrugs:** PRODRUG CHEMICAL ACTIVATION: Although a drug's derivatives are utilised for therapeutic purposes, they do not produce the necessary therapeutic results due to their high toxicity in non-target areas and poor therapeutic index.

Thus, non-toxic biofunctional chemicals are joined with the chemical moiety of pharmaceuticals with low or narrow therapeutic indices. This sort of combination enables the newly created chemical entity to work with increased activity and target site selectivity.

The utilisation of prodrugs in drug development increased as a result of this kind of combination. This prodrug's creation has been helpful since it can be more expedient and practical than researching a novel therapeutically active substance. Prodrug changes the parent drug's toxicity[24].

- 2. Genetic Prodrug Activation Mechanism:** The prodrug was given systemically while a gene encoding a drug metabolising enzyme was introduced into the cells. The prodrug is then transformed into a cytotoxic agent by the expressed enzyme.

Since prodrugs are inactive versions of active drugs, they undergo a chemical interaction inside the body to transform into the active medication. This makes it possible for the parent medication to successfully regulate the distribution of drug to the targeted spot[25].

III. NANOHYDROGEL PRODRUG FOR REDUCTION-TRIGGERED DRUG ACTIVATION AND FOR TREATING TAXANE RESISTANT MALIGNANCIES

Nanoparticle-based drug delivery systems provide benefits in reducing the impacts of cancer. The majority of cancer patients prefer chemotherapy, yet only a small percentage of them get superior therapeutic results, and the majority of cancer patients receiving chemotherapy experience negative effects. As a result, nanotherapeutic drug delivery methods have been developed, helping to improve results and lessen medication toxicity. It is now possible to employ nanohydrogels as intelligent, biodegradable, and biocompatible delivery systems at either a systemic or local location. A recently created prodrug called Hydrogelators uses a single distillation-precipitation polymerization procedure to create injectable nanohydrogels. These nanohydrogels release active substances like the cytotoxic drug cabazitaxel, which shrinks the tumour. Utilising nanogel-based treatment has demonstrated. [26]

IV. pH DEPENDENT PRODRUG ACTIVATION

- 1. Treosulfan prodrug Activation:** The pH-dependent activation of the treosulfan prodrug results in epoxide compounds. Williamson reaction occurs intramolecularly during this procedure. With the help of boric acid, the cis-diol system found in the treosulfan structure enhances complexation. Inhibition of prodrug epoxidation results from this. The $\log K_{\text{obs}} = -7.48 + 0.96 \text{ pH}$ equation for pH is satisfied by the rate constant for treosulfan activation in buffers of acetate, carbonate, and phosphate. The process is hindered if the concentration of boric acid is elevated over the treosulfan level, and the K_{obs} value decreases as the concentration of borate buffer rises. [27]
- 2. Temozolomide prodrug Activation:** A prodrug of imidazotetrazine called TMZ has been shown to be effective in treating glioblastoma multiforme. It can pass the blood-brain barrier due to its tiny size and unique characteristics. The drug's antitumor efficacy hinges on the methyl diazonium cations' pH-dependent hydrolysis, which results in methylating purine bases and DNA damage that causes cell death. In comparison to basic media, which has a pH of >7 , this medication was more stable in acidic medium, which has a pH of 5. [28]

- 3. Ascorbic Acid Prodrug Activation:** The function that ascorbic acid plays in the manufacture of collagen, which takes place in the connective tissues, indicates the antiscorbutic qualities of ascorbic acid. A donor of electrons, ascorbate. Ascorbic acid is a powerful antioxidant and reducing agent due to the capacity of ascorbate to give many electrons. Hydrogen peroxide (H_2O_2) is created via the autooxidation of ascorbate, which is pH dependant. Ascorbic acid is administered intravenously (IV) as an adjuvant in the treatment of cancer. [29]

V. PRO DRUG DEVELOPMENT AND ITS DELIVERY SYSTEMS

A prodrug is a substance with biological action that only manifests itself at various times after entering the body.

The prodrug concept has undergone extensive research and development, leading to a number of advantageous applications, including cellular permeation, solubility, chemical stability, enzymatic stability, bioavailability, toxicity, and other barrier permeations.

A prodrug that falls under more than one category is known as a Mixed-Type prodrug. Depending on the conversion processes that follow, either in concurrent or in sequential phases, the Mixed-Type molecule can be further classified as a Parallel Mixed-Type or Sequential Mixed-Type prodrug.

Classification of prodrug:

- Type I - Prodrug conversions occurs internally
- Type IA – These are those that are changed at the cellular sites where therapeutic activities are taken [30].
- Type IB: The principal metabolic tissues, such as the liver, stomach, or lung, are where the conversion takes place [30].
- Type II: The process of conversion may occur extracellularly in gastrointestinal fluids (Type IIA), the systemic circulation or other systemic extracellular fluid compartments (Type IIB), or in close proximity to therapeutic target cells (Type IIC) [30].

VI. PRO DRUG CARRIER

In order to obtain the best drug delivery to the system, the micro-nanocarriers concentrate on a few qualities that aid in developing the drug delivery system, such as hydrophilicity, biodegradability, size, shape, surface charge, and toxicity. There are several approaches to enhance the carrier designs via their therapeutic route in order to increase their therapeutic effectiveness. [31]

Many functional groups can also operate as carriers to alter the drug's structure. The follow up are some examples of the carrier [32]:

S.No.	Carriers	Name of the parent drug
1.	Esters	Diclofenac, Oleonoicacid, Oridonin, Taxoids
2.	Amides	Acyclovir, Pyrazolo[3,4-d]pyrimidine
3.	Phosphates	Propofol, Lopinavir, Chalcone
4.	Carbamates	CI-994
5.	Ether	Cadalene
6.	Carbonate	CHS8281
7.	Imine	Amphotericin B

VII. TARGETED PRODRUG DESIGN

Targeted prodrug design introduces a new strategy that helps to direct the drug design strategy to be effective for the drug delivery system. Traditional prodrug design uses nonspecific chemical approaches to mask undesirable drug properties like lack of site specificity, limited bioavailability, and chemical instability. [33]

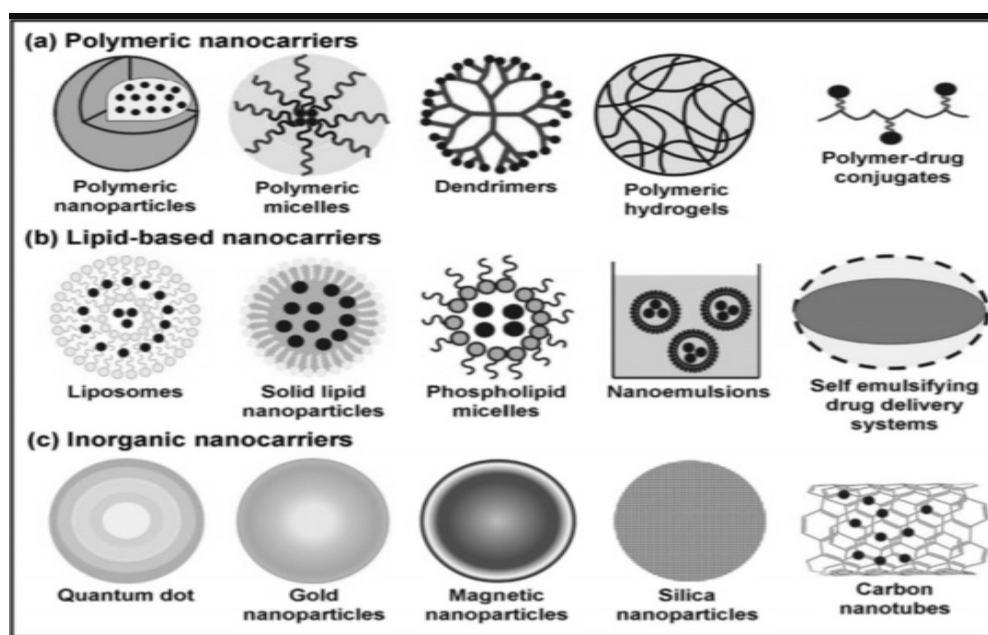
VIII. NANO PARTICLES

As we are aware, nanoparticles have become a popular alternative to functional groups as a carrier for prodrug delivery in recent years. The prodrug and nanoparticle combination may be utilised to treat cancer therapies, anti-inflammation treatments, and antiviral treatments, which results in effective drug therapy. Nanoparticles plays a vital role in reducing risk of adverse reactions. The main reason to use nanoparticle as carrier include its wide range of advantages i.e. improved stability, longer exposure duration, decreased permeation resistance.

Types of Nanoparticles;

- 1. Liposomes-the First Nanocarrier for Encapsulating Prodrugs:** Liposomes are tiny vesicles made of phospholipid bilayers that resemble membranes and are surrounded by water, Pharmacokinetics and biodistribution of a medicine, hence improving its therapeutic index.
- 2. Polymeric Nano Particle:** Another polymer-related nanosystem is that of amphiphilic block copolymer micelles. Self-assembled drug delivery systems called copolymer micelles are more biocompatible, have a better solubilization capacity, and can target tumours.
- 3. Lipid Nanoparticle:** Copolymers including poloxamers, polystyrene-block-poly(acrylic acid), and polyethylene glycol-block-poly(ϵ -caprolactone) (PEG-b-PCL) are often used to make nanoparticles. Lipid nanocarriers including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid emulsions (Les) appear promising as drug-carrier systems due to their extremely low cytotoxicity in compared to polymeric nanoparticles.

4. Self-assembled nanoparticle



A new understanding of prodrug techniques improving for in vivo and clinical applications has been made possible by nanotechnology.

Other design elements are mainly focused on the optimal release of drug but the nanoparticle has delivered to the targeted site.

Some inorganic nanoparticles have stimuli-responsive functions (triggering the release of therapeutics by utilizing their surface Plasmon resonance property) [34]

IX. CASE STUDIES IN PRODRUGS DEVELOPMENT

The two clinically validated prodrugs of propofol (an anaesthetic), phosphate ester and phosphonoxymethylpropofol. The drug release in each of these two prodrugs is started by the dissociation of a phosphoester link. The difference between the two compounds is that phosphonoxymethylpropofol has one additional oxymethylene. The bioconversion process for about half of prodrugs is the hydrolysis of an ester bond by esterases. The availability of hydroxyls and carboxylic acid activities in pharmaceuticals, as well as the ubiquitous presence of esterases, which facilitates the metabolic regeneration of drugs in the body, are two equally important factors for this. At healthy pH levels, carboxylic acid has a strongly polar functionality and is often charged [35] Initially, 5-fluorocytosine (5FC) was converted locally by cytosine deaminase (CDase) to 5-fluorouracil, a powerful anticancer medication (5FU). Due to 5FU's very variable human absorption and relatively small therapeutic window, safe administration of the drug is challenging. 5FC was inspired by its usage as a medication against CDase-expressing fungus [35].

It is advantageous that oral administration of 6-deoxy-2-aminopurine derivatives (e.g., famciclovir) with better bioavailability and absorption. encourages the creation of these substances as prodrugs that have been aldehyde or xanthine oxidase activated. This process

results in the enzymatic oxidation of 6-deoxycyclopropavir (perhaps a prodrug) to cyclopropavir, which is more effective than ganciclovir against HCMV[36].

A few examples of cutting-edge prodrug treatments include ADEPT (Antibody-Directed Enzyme Prodrug Therapy), GDEPT (Gene-Directed Enzyme Prodrug Therapy), and LEAPT (Lectin-Directed Enzyme-Activated Prodrug Therapy). Rehabilitation for Drug Use (Prodrug). Their objective is to specifically administer cytotoxic agents to cancer cells. Knowledge of the unique characteristics of the tumour microenvironment, such as pH and hypoxia, which impact the emergence of resistance, may also be used to base the delivery of active substances to the tumour [36].

X. PRODRUG DEVELOPMENT FOR SPECIFIC DISEASES OR CONDITIONS

The development of macromolecular prodrugs for inflammatory illnesses like RA is still in its infancy, in contrast to the advancements made in the creation of polymeric chemotherapeutic drugs. Although anti-inflammatory drugs' therapeutic effectiveness has been shown, there are still a number of obstacles to their macromolecularization, and their benefits have not yet been demonstrated [37].

The efficacy of 4-ASA (p-aminosalicylic acid, 4-amino-2-hydroxybenzoic acid) for the topical treatment of active ulcerative proctitis or ulcerative colitis has been demonstrated in several clinical investigations. It is more potent, more stable, and less likely to cause pancreatitis than 5-ASA, but it also has the same downside as 5-ASA: rapid and broad absorption in the upper GIT, which occurs before it reaches the colon. This is because its low acidity (pKa 3-4) causes the upper GIT to absorb it fast. Selby's research indicates that 4-ASA is a reliable and more affordable substitute for 5-ASA whether treating UC topically or when attaching to carrier molecules for release in the colon [38].

When it comes to treating IBD patients who are intolerant to 5-ASA, 4-ASA or its colon-targeted prodrugs remain obscure and unappreciated despite being more stable and effective than 5-ASA in treating UC without the obvious risk of 5-ASA-induced pancreatitis. Examining the intriguing 4-ASA molecule, exploring its untapped potential, and developing safe but efficient systems for its targeted administration to the colon are important to treat IBD as well as other local colon illnesses, such as IBS and colorectal cancer [38].

XI. CLINICAL DEVELOPMENT OF PRODRUG

Phases of Clinical Trials for Prodrug Candidates: Drugs are examined in many formats in trials for the stages to determine their effectiveness and safety. Drugs become poisonous in the body when their maximum safe level is exceeded and ineffective when their minimum effective concentration is not reached. So, to know the therapeutic level and their actions phases are highly important. The two main phases of clinical trials involved in Prodrugs are:

- 1. Pharmaceutical Phase:** The interval between the discovery of a novel chemical component and its inclusion into a drug delivery system with potential therapeutic efficacy is considered to be the pharmaceutical phase of prodrug development. It is possible to provide medications via a conventional drug delivery technique, such as

tablets, capsules, injections, creams/ointments, etc., or a novel drug administration approach, such as transdermal delivery patches or implanted devices. There are now two challenges to creating a medicinal product that can be sold commercially:

- The novel molecule's aesthetic qualities, such as odor, taste, pain upon injection, gastrointestinal irritation, etc., may restrict its utility.
- Formulation issues could surface, such as the medicine being unstable or unable to be integrated due to its physicochemical conditions[39].

- 2. Pharmacokinetic Phase:** The stage of the prodrug's pharmacokinetic process whereby absorption, distribution, metabolism, and excretion are examined. The in vivo features of a drug's disadvantages, such as insufficient absorption, extremely rapid excretion, and pre-systemic metabolism, are crucial information provided by these investigations. This phase makes it simple to assess the system's physicochemical and dosage form features [39].

Animal urine and blood samples are collected during the pharmacokinetics phase of a prodrug, and these samples are compared to the results of the previous HPLC study [40].

Future Potential and Challenges in Advancing Prodrug-Based Treatments.

Future Potential	Description
Enhanced Drug Delivery	Prodrugs hold the potential to improve drug delivery, enabling targeted and site-specific release of active drugs, maximizing therapeutic efficacy while minimizing off-target side effects
Personalized Medicine	Prodrug design innovations may open the door to personalised medicine, which would allow doctors to customise therapies to each patient's requirements based on their genetic profiles.
Overcoming Drug Resistance	Prodrugs can be strategically designed to overcome drug resistance mechanisms, enhancing the effectiveness of treatment in conditions where resistance has been a challenge
Expanding Therapeutic Range	Prodrugs may extend the therapeutic range of existing drugs, optimizing their pharmacokinetics and pharmacodynamics, potentially unlocking new applications and indications.
Improved Patient Compliance	By enhancing the stability and bioavailability of drugs, prodrugs can improve patient compliance, leading to better treatment outcomes and disease management

Challenges	Description
Chemical and Biological Stability	Ensuring the stability of prodrugs during storage and transportation, while maintaining their ability to undergo biotransformation in the body, is a key challenge in prodrug development.
Bioconversion Efficiency	Achieving efficient and selective bioconversion of prodrugs into active drugs is crucial to ensure optimal therapeutic outcomes, necessitating careful enzyme and transporter selection.
Toxicity and	The introduction of chemical modifications in prodrug design must be

Safety Concerns	meticulously assessed to avoid potential toxicity and ensure patient safety during treatment
Clinical Translation	Successfully translating promising prodrugs from preclinical research to clinical trials requires robust evidence of efficacy, safety, and scalability for regulatory approval.
Intellectual Property Issues	Intellectual property protection for prodrug innovations is crucial to incentivize and protect investment in prodrug research, but navigating patent landscapes can be complex.
Market Acceptance	Prodrug-based treatments may face challenges in gaining acceptance and adoption by healthcare professionals and patients, requiring educational efforts and evidence-based advocacy.

XII. CONCLUSION

The field of prodrug development stands as a testament to the ingenuity and perseverance of pharmaceutical research. Throughout this chapter, we have explored the diverse facets of prodrug design, activation mechanisms, delivery systems, challenges, and clinical development. From its historical roots to cutting-edge innovations, prodrug development has illuminated a path towards more effective and personalized therapies.

Prodrugs have shown their importance in improving medication distribution and therapeutic efficacy. Prodrugs are characterised as inactive or marginally active compounds that transform into active drugs following administration. The benefits of prodrug development are readily apparent in their capacity to circumvent bioavailability restrictions, enhance targeted delivery, and reduce side effects. As we explore the fundamentals of prodrug design, the relevance of structure-activity relationships (SAR), and the numerous variables affecting prodrug stability and bioconversion, we become more and more aware of the value of a methodical and logical approach.

Prodrugs can be activated via enzymatic, chemical, or pH-dependent processes, demonstrating the diversity of this discipline. The wide variety of activation mechanisms available to prodrug manufacturers makes it possible to customise treatments for certain disease stages, patient profiles, and delivery routes.

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