**"Maximizing Medication Effectiveness: The Strategic Science of Prodrugs"**

**ABSTRACT:**

A prodrug is a chemically modified, bioreversible, and inactive compound that can be modified into an active drug by metabolic reactions and can be administered into the body for its pharmacological response.

The prodrug approach has been developed to overcome the unwanted effects of certain drug properties. Prodrugs are similar to the active parent drug, but there is a small change in chemical steps. Certain prodrugs are released after the modification of active drugs by oxidation or reduction reactions. In some conditions, co-drugs are used for rapid conversion of active drugs by their metabolic reactions.

In this chapter, we have seen a general overview of the prodrug and its current strategy to improve pharmacokinetic problems and drug discovery and development. Further studies and research are going on to minimise the pharmacokinetic properties, improve the prolonged action of the drug, mask the bitter taste of the drug, and also improve the lipophilicity, water solubility, and bioavailability of drug molecules.

**Key words:** prodrug, historical findings, prodrug classification, drug design,

 **INTRODUCTION**

The biological and physicochemical properties of a prodrug characterize it. Some drugs now being used have undesirable characteristics that lead to inadequate delivery and adverse effects.

These drugs physicochemical, biological and organoleptic properties should be improved to maximize their efficacy used in clinical practice.

Many strategies have been developed during the last few decades to assist in the drug design and discovery phases. The bulk of the tactics were geared toward identifying new chemical compounds that interact most effectively with the intended receptors or enzymes while causing the fewest undesirable interactions.

Recent developments in the concept of prodrugs include the terms “**Hard drug”** and “**Soft drug”.**

**Hard drugs** are substances that lack any susceptibility to chemical or metabolic transformations in order to increase the pharmacological efficacy of a specific drug. These compounds have structural characteristics that are critical for the desired pharmacological activity.

**Soft drugs** are substances with pharmacological activity and methodical metabolism; after exerting their effects, these substances break down into inert, nontoxic metabolites and are quickly eliminated from the body. To achieve a therapeutic effect locally while preventing systemic side effects and adverse reactions, a soft drug must be developed.

This method takes a long time and costs a lot of money since it involves testing hundreds of compounds for biological activity, only one of which is approved for use in medicine. Prodrug concept is most intriguing and trustable strategies, in which the active drug is coated by a promoiety to change its negative properties.

The prodrug technique is one of the most effective modern research methods for developing more potent therapeutic drugs in the field of medicinal chemistry.

A prodrug is a dormant changed version of an active drug that is converted to an activated form after being delivered into the body via a chemical or enzymatic reaction.

Albert often used the word "prodrug" (predrug, progent) to refer to a pharmacologically inactive component that is converted to an active form inside the body.

The physicochemical and pharmacokinetic characteristics of medication (absorption, distribution, excretion and metabolism) as well as their associated toxicity, have been effectively modified using this term.

 A prodrug must go through regulated or predictable chemical and/or enzymatic biotransformation before displaying therapeutic efficacy. Instead of using a formulation method to get around obstacles, the idea uses a chemical one.



**Figure.1 schematic representation of a drug.**

In general, the immediate goal of using prodrug is to create novel entities with improved efficacy, selectivity and low toxicity.

Prodrugs are also defined as drugs with particular protective groups that counteract the negative effects of the parent drug molecules. Most prodrugs are simple chemical mimics that differ from the parent drug just slightly through one or two enzymatic or chemical reactions. Few prodrugs, however, lack a clear carrier or promoiety, yet they nonetheless generate new active drug molecules thanks to chemical alteration. Each drug candidate acts as a promoiety for the other drug candidate when two pharmacologically active drug molecules are joined into a single compound to generate a prodrug. The term "codrug" refers to this class of drug derivatives.

An ideal prodrug should undergo quick biotransformaion to its active forms and a non-toxic moiety within the body via a chemical or enzymatic mechanism.

The active drug and the promoiety must all be released either before, during, or after absorption, or in a specific target tissue or organ, depending on the action of the prodrug.

The prodrug method is now consider as one of the most promising site-specific drug delivery strategies because it makes use of endogenous enzymes and transporters that are unique to the target cell or tissue.

The anti-Parkinson agent L-DOPA is the example that was intended to increase a drug's effectiveness by accumulation into a particular tissue or organ. Dopamine is a hydrophilic neurotransmitter that rapidly undergoes oxidative deamination metabolism, which results in peripheral side effects, but does not effectively cross the blood-brain barrier. However, the Levo type amino acid transporter is made possible by the prodrug of dopamine, L-DOPA, allowing dopamine to be taken in and accumulated in the brain.



 HISTORY

In 1958, Albert introduced the term "prodrug" in his work titled "Selective Toxicity," marking its initial appearance. This concept encompasses any inactive substance that undergoes biotransformation within a living organism.

While others like Harper supported this notion, they termed it "drug latentiation," encompassing prodrugs designed for in-body biotransformation. Sometime later, Albert expressed remorse for coining an unreliable phrase and mentioned that "pre-drug" would have been a more suitable option. Interestingly, the inaugural prodrug was not originally intended as such; its actual purpose surfaced in later discoveries. Notable examples like acetanilide and phenacetin, meeting the conventional prodrug criteria, showcase their effects post-metabolism within the body.

Back in 1886, a fever-reducing medication known as acetanilide was already being utilized. This compound undergoes a metabolic transformation known as aromatic hydroxylation to become paracetamol. A similar scenario can be observed with phenacetin, where the conversion to paracetamol takes place through a process called O-dealkylation.

Acetylsalicylic acid, commonly known as aspirin, can be seen as a milder form of the prodrug salicylic acid, and it was formulated in the late 1800s by a chemist named Felix Hoffman at the Bayer Company. It was initially employed in clinical settings in 1899.

The classification of aspirin as a definitive prodrug remains a topic of debate. Methenamine and the pioneering sulfa prodrug, prontosil, offer another example of inadvertent prodrug development and how chance played a role.

 In 1899, Schering stumbled upon phenamine, an inactive precursor drug that releases antibacterial formaldehyde.

During the mid-20th century, the Parke-Davis Company purposefully modified the structure of chloramphenicol to mitigate its unpleasant taste and poor water solubility.

This marked the intentional employment of the prodrug concept. Chloramphenicol sodium succinate, boasting suitable water solubility for intravenous, intramuscular, and ophthalmic use, and chloramphenicol palmitate, utilized as a suspension for children, represent the two prodrug forms derived from chloramphenicol.Top of Form

The approach of utilizing prodrugs has proven effective with a diverse range of medications. Statistical assessments indicate that around 20% of small-molecule drugs that received approval from 2000 to 2008 were prodrugs. Furthermore, in 2008, approximately one third of all sanctioned drugs took the form of prodrugs. Presently, it is estimated that roughly 10% of all drugs available in the global market belong to this classification.

**PRODRUG CLASSIFICATION**

Derivatization and the kind of carriers a drug is attached to determine the classification of prodrugs according to conventional practise. Prodrugs are divided using this method into two sub-major classes:

(1) **Carrier-linked prodrugs** involve a scenario where the active drug candidates are temporarily connected to a carrier or promoiety through a reversible chemical bond. Upon introduction into the body, a carrier-linked prodrug undergoes a process of biotransformation, leading to the liberation of both the original drug candidate and the attached promoiety.

Typically, we select carriers that possess traits such as non-immunogenicity, cost-effective synthesis, stability when administered alongside prodrugs, and the ability to break down into inert metabolites. Another variant in this category is co-drugs, encompassing mutual prodrugs and multiple co-drugs, wherein two distinct pharmacologically active drugs are linked together to form a unified molecular entity, serving as carriers for each other.

Some examples of co-drugs are as follows:

* Indomethacin - paracetamol
* Sulfapyridine - 5-aminosalicylic acid
* 5-fluorouracil - cytarabine
* Gabapentin - pregabalin
* L-Dopa - entacapone
* Sulfamethoxazole - nalidixic acid
* Ampiciline - sulbactam

Further classifications of carrier-linked prodrugs include

(a) bipartite, in which one carrier (promoiety) is directly attached to the drug, and

(b) tripartite, in which the drug and a promoiety are separated by a spacer or connecting group.

(2) **Bioprecursors** are chemical entities that undergo subsequent metabolic transformations, leading them to evolve into active metabolites (such as the conversion from an amine to an aldehyde and then to a carboxylic acid) or potentially generate novel compounds with pharmacological activity.

 There is no carrier in this type of prodrug, but the substance should be easily metabolised to produce the required functional groups.

 The bioprecursors are converted chemically, enzymatically, or both into active drug molecules through the processes of hydration, oxidation, or reduction. Examples of these processes include lactones, which are used as some stains, dexpanthenol, and nabumetone.

 **RECENT CLASSIFICATION OF PRODRUG**

Nowadays, prodrugs are categorised based on where they are transformed into the drug molecules that are pharmacologically active. This knowledge of the site conversion process' kinetics and the contributions made by the prodrug and active parent drug to the effectiveness and safety of the product make the information extremely helpful.

The prodrugs are further divided into two groups based on the findings of this study:

* Type I and
* Type II

Prodrugs classified as Type I are those that are metabolised intracellularly (example, lipid-lowering strains, antiviral nucleoside analogues), whereas prodrugs classified as Type II are converted extracellularly, either through the systemic circulation or digestion.

Both types are again classified into sub divided types:

**Type I**

1. Type IA
2. Type IB

**Type II**

 1. Type IIA

 2. Type IIB

 3. Type IIC

Prodrugs of Type IA are transformed into their active parent drugs through metabolic processes primarily occurring in tissues like the liver. On the other hand, prodrugs of Type IB undergo conversion into their active parent drugs directly at the specific cellular sites where their therapeutic effects are exerted.

Prodrugs of Type II experience conversion outside the cells by general enzymes such as esterases and phosphatases or by enzymes specific to their intended targets. These conversions occur in various settings: within the gastrointestinal (GI) fluid environment (Type IIA), within systemic circulation or other extracellular fluid compartments (Type IIB), or even within the actual cells or tissues targeted for therapy (Type IIC).

An ideal prodrug would exhibit characteristics like high aqueous solubility, efficient transcellular absorption, and resistance to hydrolysis during the absorption phase.

 **NEED FOR PRODRUG DESIGN**

The therapeutic effectiveness and bioavailability of the parent drug must be considered prior to developing a prodrug for that drug. Both the therapeutic efficacy and bioavailability of the parent drug should be improved by a prodrug. The parameters listed below are used to design a prodrug:

1. Pharmaceutical factors that improve an active drug's solubility, chemical stability, and organoleptic quality while lowering side effects from local administration and problems related to its pharmaceutical properties.
2. Pharmacokinetic parameters increase presystemic metabolism of the active drug while decreasing absorption, time profile, and organ/tissue specific delivery.
3. Pharmacodynamic parameters increase a parent active drug's therapeutic/selectivity index while lowering toxicity or toxic effects and drug resistance.

 **PRODRUG ACTIVATION**

Prodrugs can be converted into active prodrugs either by enzymes or by chemical reactions. Most commonly, carrier-linkage prodrugs can be activated by esterase. There are many different esterase in the body, which vary in the specificity of their substrates. For example, acetyl-choline- esterase, buryl-choline esterase, and carboxyl- esterase are all present in the body.

The prodrug strategy can also be employed to control the precise release of an active compound from a prodrug at a designated location.

Carboxyl esterase (CES) enzymes are a family of enzymes whose genes are located in several tissues. They efficiently hydrolysis a variety of prodrug-containing esters and amides to the free acids.

CESs is ubiquitous in tissue expression profiles, with the highest levels of CES activity being found in the liver microsomal site.

The potential for their substrates to interact with drugs is generally considered low.

Following administration, numerous compounds undergo metabolic modifications that transform them into new active substances or intermediates that can be further metabolized into active drugs. There are five primary types of reactions involved in the activation of bioprecursors:

1. Oxidative reactions, facilitated by enzymes like CYP450, encompass processes such as:
	* O and N dealkylation (e.g., bio-precursor prodrug for alprazolam)
	* Oxidative deamination (e.g., activation of Cyclophosphamide)
	* N-oxidation (e.g., activation of procarbazine)
2. Reductive activation includes:
	* Disulfide reaction (e.g., activation of thiamine prodrug)
	* Bio-reductive alkylation (e.g., activation of mitomycin c, an anticancer antibiotic)
3. Nucleotide activation.
4. Phosphorylation activation (e.g., activation of the antiviral drug acyclovir).
5. Decarboxylation activation (e.g., Nabumetone).

These reactions collectively participate in the transformation of bioprecursors into active compounds or intermediate forms with therapeutic significance.

**IMPORTANT BENEFITS OF DRUG USE**

 Prodrugs are created to increase the bioavailability of drug candidates, thereby reducing the physicochemical, physicokinetic and pharmaceutical issues. The following list includes some important advantages of prodrugs:

* Improvement of bioavailability through
1. Enhanced aqueous solubility
2. Enhanced lipophilicity
* Improved parenteral administration
* Site-selective/targeted drug delivery in the case of

1. Central nervous system (CNS) drug delivery

 2. Tumour targeting

3. Liver-targeted delivery

* Prolongation of drug action
* Reduction in toxicity
* Improvement in patience compliance/masking taste or odour

**IMPROVEMENT IN BIOAVAILABILITY**

In most cases, increasing bioavailability is the main objective of prodrug synthesis. Some significant physicochemical factors play a role in the oral bioavailability of potential drugs during drug development, including such as suitable lipophilicity, suitable aqueous solubility, and extensive hepatic metabolism, permeability, and excretion, which are acid-base properties of the molecules have a significant impact.

**Enhanced Aqueous Solubility**

The library of drug candidates produced since the introduction of combinatorial chemistry and high through-out screening techniques has poor water solubility. Prodrugs provide a different method to get around solubility restrictions in such circumstances.

Only a few water-soluble prodrugs designed specifically for oral administration have been created to date. Polar structures can be added to increase solubility in water, allowing for parenteral or oral administration. Additionally, by reducing the crystal packing or altering the parent drug's melting point, improved water solubility and better oral bioavailability may be attained.

**PRODRUG TO IMPROVE LIPOPHILICITY**

 To facilitate the administration of drugs via various routes such as oral, ocular, or topical delivery, prodrugs are employed to enhance their lipophilicity.

 The primary purpose behind creating prodrugs is to enhance factors like oral bioavailability and intestinal absorption, achieved by concealing the drug's polar components. An example is dabigatran, a potent thrombin active site inhibitor with a logP of 2.4 (n-octanol/buffer pH 7.4), which suffers from notably low oral bioavailability.

 To address this, the initial substitute for oral warfarin, dabigatran Etexilate, was developed as a prodrug of dabigatran. Esterases facilitate the transformation of dabigatran etexilate from its oral form to the active dabigatran drug. The oral bioavailability of dabigatran Etexilate stands at 6.5%.

**Ophthalmic drug delivery**

For ocular absorption enhancement, lipophilic prodrugs are also employed. For instance, latanoprost and travoprost, isopropyl esters of their respective carboxylic acid forms, exhibit higher lipophilicity and can effectively penetrate the corneal epithelium.

**Topical drug delivery**

Lipophilic prodrugs are also beneficial in improving the transdermal absorption of specific drugs in topical applications. For example, increased lipophilicity in ester prodrugs allows for their accumulation in the skin, heightening effectiveness while minimizing side effects.

This is particularly relevant for topical corticosteroids, commonly used for skin problems. Fluocinolone-acetone diester prodrugs, display favourable traits like high membrane retention (within the epidermis) and low permeability, making them suitable for topical corticosteroid use.

 The higher lipophilicity of the fluocinolone acetonide prodrug enhances its potency compared to the less lipophilic fluocinolone prodrug.

This advanced application of lipophilic prodrugs showcases their significance in optimizing drug delivery across various routes and addressing challenges associated with bioavailability and absorption

 **ADVANCED PAENTERAL MANAGEMENT**

Parenteral or injectable drug administration is the preferred route of drug administration management in various clinical settings. Multiple successful prodrugs with better water-soluble properties available for parenteral administration.

The addition of a water-solubilizing effect through a prodrug-based approach commonly involves introducing an ionizable or polar promoiety to the original drug molecule.

The attachment of a dianionic phosphate group, for instance, often leads to a substantial increase in solubility, sometimes spanning several orders of magnitude. A number of phosphoric acid esters have been developed as potential water-soluble prodrugs, particularly for parenteral administration, and to a lesser extent, for oral administration.

A specific example is the phosphoethyl spacer prodrug associated with the amine group of phenytoin, an anti-epileptic drug. This prodrug demonstrates a remarkable 7500-fold increase in aqueous solubility, reaching 140 mg/ml, as opposed to the original drug's solubility of 0.019 mg/ml.

 This marked enhancement in solubility can greatly impact the drug's effectiveness, particularly for administration routes that rely on water solubility.

Fosphenytoin is a phosphate ester of fluconazole, which is a broad spectrum anti-fungal drug that is parenterally administered.

The higher aqueous soluble solubility (more than 300 mg/ ml) of this ester is attributed to lower bolus and higher intravenous dosing volumes. Propofol phosphate (a phosphate ester) is a propofol-intravenous ester that increases aqueous soluble propofol by 150 mg/ ml. On After intravenous administration, bioconversion is rapidly decreased compared with phosphoethyl propofol or phosphonooxy methyl propofol, which is an anaesthetic drug.

**SITE-SELECTIVE/TARGETEDDRUG DELIVERY**

The ultimate objective of drug delivery is site-specificity, which guarantees an accurate and direct action at the place of action without exposing the remaining tissues to adverse effects.

This may be the most promising potential of prodrugs. Prodrugs are converted into their active form only in the intended organ/tissue, either by the use of specific enzymes or by the use of a pH value other than the normal one for activation.

When a drug's lipophilicity is elevated, it would improve the passive and non-specific transport of the drug to all tissues.

**Central Nervous System (CNS) Drug Delivery**

The clinical advancement of drugs targeting the central nervous system (CNS) is frequently impeded by the challenge of ensuring effective passage across the Blood-Brain Barrier (BBB) while maintaining their therapeutic efficacy. The BBB plays a vital role in maintaining an optimal chemical environment for proper brain function. Understanding the intricate transport mechanisms and enzymatic activities at the BBB can significantly enhance the delivery of therapeutic agents to the CNS compared to other parts of the body.

For instance, in the treatment of Parkinson's disease, dopamine prodrugs are used to address this issue. An amino acid analog and the precursor of dopamine, L-DOPA, serves as an illustrative example. This compound can be transported to the brain through the influx transporter LAT1 , enabling it to cross the BBB effectively. However, dopamine, due to its hydrophilic nature, is unable to traverse the BBB on its own.

The complexities of the BBB present a formidable challenge, but understanding its intricacies and developing innovative prodrug strategies can greatly improve the delivery of therapeutic compounds to the CNS, ultimately benefiting patients with conditions like Parkinson's disease.

**Tumour Targeting**

One of the prevalent strategies for enhancing the concentration of a drug within the central nervous system (CNS) involves augmenting its lipophilicity compared to the original parent drug. When a drug's lipophilicity is heightened through the creation of a new prodrug, it facilitates the drug's penetration and access into the CNS.

The primary goal of cancer therapy is to enhance the targeted delivery of active substances specifically to tumor cells while minimizing harm to healthy cells. Achieving tumor specificity can be accomplished through the use of enzymes, transporters, or by developing prodrug antibodies that are specifically recognized by tumor cells.

 An added advantage is that these preparations can often be administered orally. An illustrative example involves the prodrug 5-FU, which is administered orally and requires a sequence of three enzymes for its conversion into the active drug.

Following oral administration, 5-FU exhibits nearly 100% bioavailability, reaching its maximum concentration (T-max) within approximately 1.5 hours. Thymidine phosphorylase, which is considerably more active in tumor cells compared to normal cells, then selectively releases 5-FU into the tumor cells.

To expand the range of treatable tumors using enzyme-prodrug therapy, two prominent approaches are employed: Antibody Directed Enzyme Prodrug Therapy (ADEPT) and Enzyme Prodrug Therapy with Gene (GDEPT). These approaches aim to address challenges associated with tumor selectivity.

In ADEPT, an antibody targeting a tumor antigen is developed and linked to an enzyme. When administered into the bloodstream, the antibody-enzyme complex selectively binds within the tumor. In contrast, GDEPT involves administering a prodrug into the bloodstream, which is converted into a cytotoxic metabolite by the enzyme.

The selectivity of the approach is determined by the tumor specificity of the antibody. Furthermore, prodrug administration is strategically delayed until a substantial difference in enzyme levels between the tumor and normal tissue is observed. These strategies highlight innovative ways to enhance tumor-specific therapy and minimize adverse effects on healthy cells.

**Liver-Targeted Delivery**

Of all the organs, the liver could be the most effective for organoselective drug delivery because it's a metabolic organ and has a wide range of enzymes with specific metabolites that activate prodrugs.

**PRODRUGS FOR LONGER DURATION OF ACTION**

Short half-life drugs often require frequent dosing to maintain stable blood concentrations, which can lead to poor patient adherence and fluctuations in drug levels. Prodrugs with extended half-lives offer a solution to these issues.

Long-acting antipsychotic drugs play a crucial role in symptom control and relapse prevention. They improve patient compliance and treatment effectiveness. A case in point is Fluphenazine Decanoate, a prodrug in the form of a long-acting Intramuscular Depot Injector (IDI) used for schizophrenia treatment. This prodrug is administered every 2 weeks, ensuring sustained therapeutic levels.

Prodrugs with prolonged action are also termed "depot" prodrugs. This approach is exemplified by the requirement for extended analgesia in patients with moderate or severe pain, such as postoperative or burn pain, for up to 3 days following trauma. This underscores the need for depot analgesics that offer prolonged relief.

Prodrugs that are longer in duration of action are BUPENORPHINE DECANANATE, ENANTHATE, and PROPIONATE. These prodrugs were synthesised and formulated in SESAME OIL FOR I.M INJECTION. Pharmacokinetic studies of BUPENOURPHINE DECANATE showed that it produces 4.1 days of action. This is 14 times longer than the traditional.

**REDUCTION OF TOXICITY**

The utilization of prodrugs has demonstrated efficacy in mitigating the toxicity of various drugs, particularly those with minimal or negligible toxicity. A prime illustration of this is seen with the antiretroviral antibiotic doxorubicin, widely employed as an anticancer agent, but hampered in its application due to its cardiotoxic effects. As a result, it became imperative to develop a drug delivery system that would enhance doxorubicin's presence in tumor tissue while diminishing its accumulation in cardiac tissue.

This challenge was addressed through the creation of a galactoside prodrug, specifically activated by the enzyme β-galactosidase. The hydrophilic portion of this prodrug prevents its dispersion to non-targeted tissues, leading to a more efficient prodrug that maintains lower concentrations in cardiac tissue compared to the parent drug.

 This innovative approach exemplifies how prodrugs can be engineered to enhance drug effectiveness while minimizing detrimental effects.

**PROTECTING FROM RAPID METABOLISM AND EXCRETION**

Prodrugs play a crucial role in blocking specific sites or functional groups within a molecule that are susceptible to pre-systemic metabolism, thereby leading to an increase in oral bioavailability.

For instance, Naltrexone, a potent analgesic utilized to manage moderate-to-severe pain, faces limited oral bioavailability at just 17% due to 3-hydroxylation, a metabolic pathway where naltrexone is susceptible. To address this, naltrexone is synthesized as naltrexone acetylsalicylate, functioning as an ester-prodrug. This modification enhances oral bioavailability by a factor of 5 in dogs.

Similarly, Estradiol and ethinyl Estradiol suffer from low oral bioavailability because of conjugation at the phenolic hydroxyl position. To counter this, the estrogen sulfamate prodrug was developed, involving the substitution of the phenolic hydroxyl group with a sulfamate.

This sulfamate prodrug effectively shields estrogen from the liver's first-pass effect, leading to increased systemic activity of orally administered estrogens. These examples underscore the strategic utilization of prodrugs to optimize the oral delivery of therapeutic agents.

**IMPROVEMENT OF TASTE**

Taste is a significant factor in the formulation of pharmaceutical dosage forms, and masking the bitter taste of oral drugs is of utmost importance to ensure patient compliance, particularly among pediatric and geriatric populations. Various technologies have been developed to mitigate this issue, including physical barriers, chemical and solubility modifications, and solid dispersion techniques.

Chemical modifications aimed at reducing interactions with taste receptors can be achieved through the prodrug approach. For instance, Paracetamol (also known as acetaminophen), a commonly used antipyretic and pain-relieving drug, possesses a bitter taste.

This bitterness is attributed to the interaction between the phenolic hydroxyl group of Paracetamol and bitter taste receptors via hydrogen bonding. By blocking Paracetamol's hydroxyl group using an appropriate linker, the interaction with taste receptors can be inhibited, resulting in the removal of the bitter taste. Research conducted on the synthesis of Paracetamol prodrugs that lacked the bitter taste sensation.

Similarly, Cefuroxime, an antibacterial agent, is known for its intensely bitter taste. This bitterness arises primarily from an interaction between the iso-butyric acid group located at position 3 of the molecule and the active site of bitter taste receptors.

Incorporating prodrug strategies to modify the chemical structure of drugs offers a valuable tool for addressing taste-related issues, thereby improving patient acceptance and adherence to medication regimens.

**IMPROVEMENT OF ODOUR**

Drugs with high vapour pressure or a low boiling point tend to have an unpleasant odour, making them difficult to formulate. For instance, ethylmeraptan, a tuberculosis bacterium agent used to treat leprosy, has an unpleasant odour due to its low boiling point of 25°C. Ethylthiol esters are the most attractive prodrugs, and a diethyl-dithiol-isophthalat prodrug has been developed from ethyl-meraptan . This prodrug has been found to be highly effective and odourless.

**MINIMIZING PAIN AT INJECTION SITE**

Injection site pain is caused by the precipitation of drugs, which can cause cell lysis and tissue injury. This may be due to the composition of the vehicle or the pH of the vehicle needed for formulation.

For instance, the medication phenytoin, which is approved to treat status epilepticus, has poor solubility in water, and the pH must be adjusted to 12 for injection, which can lead to soft tissue damage and pain at the injection site due to phenytoin precipitation.

Propofol is a highly lipid soluble drug, making it difficult to develop injectable formulations. The only available formulations are oil-in-water emulsions, which can cause pain on the injection site.

In 1996, the Food and Drug Administration (FDA) approved the phosphoester prodrug propofol, which is a water-soluble form of propofol.

Fospropofol is a propofol prodrug that is 100% bioavailable intramuscularly.

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