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A Brief Overview on Prodrug and Its Design

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ABSTRACT

Prodrugs are reversible chemical modifications of active drugs designed to improve molecules pharmacokinetic, pharmacodynamic or pharmaceutical properties. These chemical modifications improve the properties of the drug such as permeability, solubility, chemical or metabolic stability, thus enhancing its absorption and bioavailability typically. Ideally, a prodrug is pharmacologically inactive and efficiently converted through in vivo enzymatic and/or chemical transformations to the active parent. The prodrug's bioconversion releases the active drug and a promo that is preferably physiologically inert and readily removed. In this review, we discussed in detailed about prodrugs and their delivery.

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INTRODUCTION

Prodrugs are covalently bonded inactive and drug precursors which are chemically modified. It has a weak link between a drug and inert chemicals that can be broken to supply medication. To provide a therapeutic effect, the connection may be broken in the body through the enzymatic or non-enzymatic operation. There are different terms used to describe constructive, congeneric, licentiate and reversible or reversible pharmaceutical materials. The design approach is referred to as drug latentiation or simply the latentiation process. The drug consists of active drug and promoeity. The latter is not necessary for pharmacological action but is carefully selected to transfer a desirable property to the drug, resulting in the compound with the desired pharmacological property.

Prodrug may exist naturally, such as many phytochemicals, botanical components, and endogenous content or maybe synthetic or semi-synthetic derivatives deliberately generated as part of a rational drug design or incidentally, during drug development, The release of active drug may occur before, during or after drug absorption or at a specific site of action in the body need on the purpose for which it is designed.

The prodrug can be converted into pharmacologically active compounds. Mostly one or more metabolites have a similar pharmacological profile to other parent drugs and some are responsible for ADR. Therefore, it is of therapeutic concern the duration and intensity of the reaction to a drug-related to the time course of all active substances in the body, the pharmacokinetics of active metabolites as well as that of the administered compound.

Prodrug concept

The basic objective of prodrug design is to mask undesirable drug properties such as low water or lipid membrane solubility, low target selectivity, unwanted taste, irritation or pain after local administration, systemic metabolism and toxicity. Generally speaking, the rationale behind using prodrugs is to enhance parent drugs ' absorption, distribution, metabolism, excretion, and unintended toxicity. The term prodrug, coined by Adrien Albert in 1958 classically refers to biologically inert derivatives of drug molecules undergoing *in-vivo* enzymatic and/or chemical transformation *in-vivo* to release the active form of the drug. The active medication is released before, during or after the drug has been absorbed from its inactive form. Most medications are released only after their activities have met goals. A drug can improve a parent drug's bioavailability and therapeutic efficacy. While the word prodrug

is now common, it has also been referred to as reversible or reversible derivatives or conjugates of billable drug carriers.

Objectives to develop prodrugs: [6]

There are three fundamental intersecting objectives in prodrug research:

1. Pharmaceutical: To enhance solubility, chemical stability, and organoleptic properties; to reduce discomfort and/or pain following local administration, and to minimize problems related to active agent pharmaceutical technologies.

2. Pharmacokinetic: improving the absorption (oral and non-oral routes), decreasing the systemic metabolic rate, improving the time profile, raising the active agent's organ/tissue-selective delivery.

3. Pharmacodynamics: to minimize toxicity and increase the therapeutic index, to create a single chemical entity combining two drugs (co-drug strategy).

Ideal drug requirements of prodrugs: [7,8]

• No intrinsic pharmacological action should be exhibited.

• Where needed, it should undergo rapid chemical or enzymatic metabolism into an active form.

• In contrast to the active drug, metabolic fragments should be non-toxic.

Types of prodrugs:[9,10,11]

1. Carrier linked prodrugs: The active molecule (the drug) is temporarily bound to a carrier (also known as a promo) through a reversible covalent association in the carrier-linked prodrugs. Once in the body, the carrier-linked drug is biotransformed, releasing both the parent drug and the carrier. The carrier should ideally be non-immunogenic, easy to synthesize at low cost, stable under drug administration conditions, and biodegraded to non-active metabolites. The carrier linked Prodrugs are further categorized as follows:

a. Bipartite Prodrug: A link between the carrier and the molecule of the drug is established.

b. Tripartite Prodrug: A connection between carrier, linker, and drug will be formed here.

2. Photoactivated prodrug: A photoactivated Prodrug is a compound that is activated by irradiation with visible light or long-wavelength UV (UV-A) specific wavelength. UV radiation generally activates the energy of the drug to interact with several cellular substratum mechanisms. This therapy is referred to as photodynamic therapy (PDT) for treatment. Special lasers, lamps, optical fibers are required to target concentrate focus concentrate direct guide focused aim More radiation on specific organs or tissues in the body.

3. Antibody directed enzyme prodrug therapy: Antibody directed enzyme Prodrug therapy used to specifically target cancer cells in an attempt to develop drugs. This method is based on enzyme activation of Prodrugs. It uses a conjugate antibody-enzyme to deliver the target enzyme. Once the enzyme concentration enters the tumor site, Prodrug reaches the tumor and is converted to the active drug by the enzyme carried by the antibody.

4. Bioprecursor prodrugs: the bioprecursor produces new compounds by molecular modifications of the active principle. Such prodrugs include embryos of active species within their structure and the metabolism of which gives rise to an active drug. The main difference is that they do not contain any carrier.

5. Hard prodrug: A hard Prodrug is a biologically active agent with a high lipid solubility or water solubility with a long half-life eg: cocaine and heroin.

6. Soft prodrug: A soft Prodrug is a biologically active agent that is quickly and reliably converted into non-toxic molecules in vivo. Eg: adrenaline and insulin.

The prodrugs can be further divided into two groups based on their conversion site into the pharmacologically active agent:

Type I – Intracellular metabolization:

Type IA pro-associated medications (e.g., acyclovir, cyclophosphamide, 5-fluorouracil, L-DOPA, zidovudine) are metabolized at their therapeutic activities of cellular targets.

Type IB prodrugs (e.g. carbamazepine, captopril, molsiinterdomine, primidone) are converted by metabolic tissues, i.e. by the liver, into parent drugs.

Type II – Extracellular metabolization:

Type IIA – in the gastrointestinal fluid system (e.g., loperamide oxide, sulfasalazine).

Type IIB – in the circulatory system and/or other compartments of extracellular fluid (e.g. aspirin, bambuterol.

Type IIC – near or inside the therapeutic targets of cells (ADEPT, GDEPT). Some prodrugs belong to more than one class and are called as mixed prodrugs.

Goals of prodrug design

A. Formulation and pharmacokinetic aspects: Pharmaceutical goal involves overcoming the following unpleasant taste when given oral, pain on injection, low solubility, slow dissolution rate. The pharmacokinetic goal involves overcoming Poor bioavailability, short duration, high first-pass metabolism, toxicity or side effects, non-specificity.

B. Conversion site: The main objective of all Prodrugs is that after the specific problem has been identified they should be quantitatively converted to a drug. The full conversion of Prodrug to the active drug should take place immediately after the identification.

C. Bioavailability: Prodrug absorption should be rapid and its conversion in blood should be instantaneous if the goal is to increase the bioavailability.

D. Prolonged duration and stability: The duration of drug in plasma is determined by 2 steps The input of Prodrug from the site of administration to blood. The conversion of Prodrug to the drug in the blood.

The stability of prodrugs is required in two areas. They are Gastrointestinal tract and At storage.

Applications of prodrugs:[12-16]

A. Reduction of toxicity: The toxicity of the drug can be minimized by using the formulation of Prodrugs. Methotrexate an antitumor drug affects both healthy cells and tumor cells equally, but it is poly(L-lysine) derivative is only toxic to tumor cells.

B. Prolonged action: When the half-life of the plasma is reduced, high clearance from the body may result in regular dosing, but Prodrug can prolong the action to a few months or more.

C. Improvement in patient compliance: Generally, patients will not take medicines that are unpalatable in taste and odor. This means that saliva solubility and in turn contact with taste buds can be minimized by esterifying drugs with long-chain fatty acids.

D. Targeted drug delivery: Site-specific drug release results in maximum drug absorption avoiding toxicity in the non-target area associated with drug availability as well as early drug biotransformation. The second approach used to improve target drug delivery is to change the drug's hydrophilic or lipophilic properties / coupling the drug with a different site-specific carrier molecule to target drug location.

E. Increase insolubility: Prodrugs are used in poorly soluble drugs to improve their solubility. Eg: Methylprednisolone is converted to methylprednisolone sodium succinate.

F. Increase in bioavailability: Increase in lipophilicity leads to increased passive transport, so its bioavailability can be improved by imparting lipophilic carrier to a product. Example Acyclovir is converted into 6 deoxy acyclovir which is 5-6 times more bioavailable and 18 times more water-soluble compound than the parent.

Limitations of prodrugs:[17-20]

(i) Formation of a toxic prodrug(carrier-mediated) metabolite which is not produced from the drug.

(ii) Uptake of a vital endogenous component during the metabolic process.

(iii) Generation of a toxic metabolite from the “inert” carrier moiety.

(iv) Release of endogenous modifiers (causing enzyme induction, displacement of protein-bound compounds, etc).

CONCLUSION

The drug strategy is one of the most promising approaches for improving therapeutic efficacy and/or reducing the adverse effects of pharmacologically active agents through various mechanisms, including increased solubility, stability, improved permeability and bioavailability, prolonged biological half-life, and tissue-targeted delivery. Their importance is supported by the growing percentage of approved new drug entities, which are prodrugs. Despite the significant progress made in the field of prodrug design, more studies are needed,

particularly at the early stages of drug discovery, to achieve the desired state of the art and take its place in modern pharmacotherapy.

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