A Review Article: Advanced Concepts In The Prodrug Design

Omar A. Yousif * * Pharmacy Department, Baghdad College for Medical Sciences, Iraq

Imad M. Malik Al-Rubaye * * Pharmacy Department, Baghdad College for Medical Sciences, Iraq
Email ID: imad.muneeb@bcms.edu.iq

ABSTRACT

Prodrugs are chemically improved compounds used in the treatment approach because of their valuable physicochemical characteristics (better stability, enhanced solubility, improved permeability) applied in an inactive form. The biological effect is applied by the active compounds obtained via chemical or enzymatic activation (biotransformation). About (10-15)% of drugs were designed as suitable prodrugs and about 50% were then transformed into active compounds through hydrolysis, mainly via ester hydrolysis. Prodrug Design aims to advance the compounds' bioavailability by overcoming unwanted features and lowering the first-pass metabolism. Also, other purposes include improvement of the compound absorption, prolongation of action duration or improvement of selectivity to the target. Types of prodrugs include Classic, Bioprecursors, Targeted, Mixed Prodrugs and Mutual Prodrugs.

Keywords:

I - Introduction:

The clinical use of most drugs may be limited due to pharmacological, physicochemical and toxicological properties. Prodrug strategy almost provides improving the physicochemical characteristics of a drug. The aim of the prodrug strategy as an alternative for optimizing agent efficiency has been enhanced. The prodrugs: lovastatin, enalapril, acyclovir and omeprazole are good examples. [1-6]

Prodrug design includes a molecular modification to signify any compound requiring chemical or enzymatic biotransformation before providing its pharmacological effects, and the active form is obtained at or near the action site. Previously, prodrug strategy was only related to drugs target and their pharmacokinetics. Recently, advanced prodrug strategy has become one of the most excellent and valuable strategies for developing new drugs such as anticancer agents [7,8].

Many reasons that rationalize the necessity for prodrug design by drug molecular modification: [9-10]

- Pharmaceutical difficulties: decreased chemical stability, unacceptable taste, formulation problems, pain and high irritation
- Pharmacokinetic difficulties: decreased oral absorption, polarity, low solubility, increased rate of pre-systemic metabolism, decreased bioavailability by non-oral administration methods, decreased target selectivity and short time profile.
- Pharmacodynamic problems: narrow therapeutic index, selectivity lack at the action site.

The prodrugs are classified into:

- Classic Prodrugs: [1,2,9,12]

Classic prodrugs are inactive (or much less active than the drug). The active drug would be released and free due to the chemical or enzymatic prodrug hydrolysis. An active drug is linked to a proper moiety to provide or improve

selectivity, bioavailability, prolonged action duration and lowered toxicity. Also, some prodrugs are used to improve or overcome drug formulation problems. The main aim of classic prodrugs includes bioavailability improvement. The use of a suitable moiety is required to improve liposolubility or hydro-solubility. The ester prodrugs of ampicillin are good examples of classic prodrugs. Absorption of ampicillin is about 40% because of high polarity resulting in high hydro-solubility. Lipophilic acyloxy-alkyl esters were used and improved absorption to around 90%, increasing ampicillin bioavailability. When the prodrugs are absorbed, ampicillin is obtained in approximately 15 minutes. Also, hydro-solubility can be enhanced by lowering inter or intra-molecular hydrogen bonds because those interactions provide highly organized structures, causing lower hydro-solubility. Hydroxymethyl derivatives (such as amides) of acidic drugs can increase aqueous solubility.

- Bioprecursors: [9,12-14]

Bioprecursor is a prodrug category designed to improve a drug's pharmaceutical, pharmacokinetic or pharmacodynamic limitations that limit its clinical use. The bio-precursor does not require linking to a carrier moiety; it is prepared via a structural alteration of the active compound. This modification produces a new compound transformed through enzymatic or chemical metabolism, and the formed compound becomes active.

Lovastatin is active because of its biotransformation (metabolism) to an open-chain non-lactone active metabolite. The lactone form produces a further proper partition coefficient for the drug, and the carboxyl group should be obtained to cause a comparison with the substrate of the enzyme.

Levodopa is another crucial example of a bio-precursor prodrug. Levodopa can pass the blood-brain barrier and act as an immediate dopamine precursor.

- Targeted Prodrugs: [15, 16]

Targeted prodrug strategy is a new strategy that provides direct and effective drug delivery. Recently, this design has increased interest. In these prodrugs, the carriers have an essential importance because of their selectivity, which they must have, because they would interact with enzymes or receptors placed in cells.

Targeted Prodrugs can provide site-specified drug delivery or site-specific drug bioactivation. Doxorubicin (Tumor Targeting), Zidovudine (Brain Targeting), γ glutamyl levodopa (Kidney Targeting), and Sulphasalazine (Colon Targeting) are good examples of Targeted prodrugs.

- Mixed Prodrugs: [17,18]

These prodrugs have bio-precursors and classic prodrugs features, needing chemical or enzymatic biotransformation and enhancing drug concentration in a specific site of action. In some cases, the designed carrier needs chemical or enzymatic biotransformation before its absorption. For example, this design is applied to compounds that act in the central nervous system. In this design, a reduced form of methyl-nicotinic acid (the carrier) requires biotransformation by an oxidative enzyme system before passing the blood-brain barrier. When the prodrug is positively charged, it will be difficult to cross back through the blood-brain barrier, and the prodrug would be highly concentrated in the brain. The prodrug concentration in the brain provides high efficacy and reduced drug toxicity.

- Mutual Prodrugs: [19-22]

Mutual Prodrug strategy is a design of carrier-linked prodrug, where the added carrier is also a biologically active agent instead of the inactive moiety. These prodrugs include two or more compounds where one is used as a carrier for the other. The aim includes promising to provide similar or different therapeutic activities leading to higher individual effectiveness or synergistic effect. For example, a k-carragenan-3'-azido-3' desoxytimidine, a zidovudine polymer mutual prodrug o, in which the carrier a-carragenine has a considerable anti-HIV activity.

II- Conclusion:

Developing a prodrug design is one of the recent medical research's exciting and effective strategies. Prodrug design should be applied to advance drug delivery and/or pharmacokinetics, target the required drug to specific tissues or cells, or lower toxicity.

Although the prodrug design can be very challenging, the prodrug strategy provides a suitable method to overcome the unwanted properties of drugs. Prodrug design is an effective technique to increase the bioavailability of drugs. Recent therapy challenges include target drug delivery, particularly in cancer treatment.

III- References:

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