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Prodrug: Design and Its Applications

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Commentary Article

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PRODRUG

Prodrugs, metabolites of drugs, targeted drugs are commonly used in the pharmaceutical field. Prodrug is used to signify pharmacologically inactive chemical moieties which are used to alter the physiochemical properties of drugs temporarily in order to improve their efficacy and reduce their toxicity [1 - 3].

Prodrugs are bioreversible derivatives of drug molecules which undergo chemical transformation or enzymatic conversion in vivo to release the active parent drug which shows desired pharmacologic effect. In both drug discovery and development, prodrugs have become an established tool for enhancing biopharmaceutical, physiochemical, or pharmacokinetic properties of therapeutic agents. The use of a prodrug is widely encouraged to optimize absorption, distribution, metabolism, and excretion (ADME) processes [4 - 11].

Pharmaceutical scientists are often facing serious formulation problems such as poor solubility, poor organoleptic properties and chemical instability. Due to delayed pharmaceutical solution to solubility or stability problem, scientists preferred to take advantage of a produg strategy.

Prodrugs are usually designed to enhance oral bioavailability due to poor absorption from the gastrointestinal tract. The prodrug strategy has been used to improve the selectivity of drugs. Prodrug Design improves bioavailability, aqueous solubility, palatability and also gives protection against fast metabolism [12 - 16].

Prodrugs for Site Specificity

Site-specific drug delivery helps for accurate and direct effects at the site of action without subjecting the remaining tissues to significant levels of the active agent. When the lipophilicity of a drug is increased, it would enhance transportation of the drug passively and nonspecifically to all tissues.

Prodrugs for (increased) site specificity

To increase the site specificity of certain drugs, the following means of preparing prodrugs are used:

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1. Increase or reduction in volume
2. Alteration of hydrophilicity or solubility
3. Introduction or removal of cationic or anionic moieties
4. Change of pKa
5. Incorporation of hydrocarbon or other suitable stable or labile moieties, and carriers that transport the compound to specific organs or tissues and make it to accumulate selectively there, where it is bioactivated.

Prodrugs for GIT

A nice objective of using prodrugs is to restrict the drug action to the upper part of the GIT. If we want to target drugs against an infection of the GIT, then we should prevent the drugs being absorbed into the blood supply. For example retardation of the drug absorption, as in case of sulfathiazole can easily be done by using a fully ionized molecule which is incapable of crossing cell membranes. The incorporation of strongly hydrophilic moieties to the sulfonamides prevents their transport to the bloodstream. They are incapable of crossing the gut wall and are therefore directed efficiently against the GI infection.

Prodrugs for Masking The Bitter Taste of Drugs

Pharmaceutical companies are recognizing the significance of masking the taste for concealing the obnoxious taste [17]. Bitter taste receptors protect the organism against the ingestion of harmful substances. Bitter masking agents [18 - 22] are diverse in their physicochemical properties and chemical structure [23, 24]. In humans, bitter taste perception is mediated by 25 G-protein coupled receptors [25]. Drugs such as non-steroidal anti-inflammatories, macrolide antibiotics, and penicillin have a pronounced bitter taste [26].

Enzymes for Bioconversion of Prodrugs

The mechanism of proton transfer between two oxygens in Menger's rigid carboxylic amides has led to the design of prodrugs that mask the bitter taste of dopamine, atenolol, amoxicillin and cephalexin, The role of the linker in these prodrugs is to block the free amine group in the parental drug and to enhance the release of a drug in a well-defined manner [27 - 34].

The striking efficiency of enzyme catalysis has inspired many organic chemists to explore enzyme mechanisms by studying certain intra molecular processes such as enzyme models which proceed faster than their intermolecular counterparts. This research brings about the important question of whether enzyme models will replace natural enzymes in the conversion of prodrugs to their parental drugs [35].

Enzymes are mandatory for the inter conversion of many prodrugs to their parental drugs. Among the most important enzymes in the bioconversion of prodrugs are amides (eg. trypsin, chymotrypsin, elastase, carboxypeptidase, and aminopeptidase) and ester-based prodrugs (ex. paraoxonase, carboxylesterase, acetylcholinesterase and cholinesterase). Most of these enzymes are hydrolytic enzymes, however, non-hydrolytic enzymes, including all cytochrome P450 enzymes, are also capable of catalyzing the bioconversion of ester and amide-based prodrugs [36 - 40].

Modern computational methods can be used for the design of innovative prodrugs for drugs that contain hydroxyl, phenol, or amine groups [41 - 45]. For example, mechanisms of some enzyme models that have been used to gain a better understanding of enzyme catalysis have been recently investigated and utilized for the design of novel prodrug linkers [46 – 51].

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CONCLUSION

Prodrug approach has been used to overcome undesirable drug properties and to optimize the clinical drug applications. Prodrug approaches enhanced solubility, site specificity, prolonged release and toxicity limited bioavailability. Nowadays, the modern computational design uses a design of linkers with bitter tasting drugs to release the parental drugs in a well-defined manner. Thus the rate of release of the parental bitter tasting drugs will be controlled. Site specific targeting with prodrugs can be improved by the use of gene delivery with the help of enzymes and transporters. Thus produg design is widely used in the development of selective drug delivery systems.

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