Metabolic Considerations in Prodrug Design: An Overview

Abstract: The review of metabolic considerations in Prodrug design is a well-established dedication to the design of absolutely safe drugs by targeting the biopharmaceutical, physiochemical and pharmacokinetic properties. Its scope extends to the improving poor drug properties such as stability, permeability, solubility and toxicity by approaching through physical, chemical or biological ways. The review covers how metabolic consideration is helpful in prodrug design.

Keywords: Prodrug Design, physiochemical, pharmacokinetic, metabolic.

INTRODUCTION

Prodrug design is productive approach for drug targeting by switching the biopharmaceutical, physiochemical or pharmacokinetic properties. Prodrugs are active therapeutic chemical agent, which must undergo modification in vivo to release the active drug.

Design of Prodrug:

Prodrugs are compounds, which are inactive but are converted in the body to the active drug:

- Acid sensitivity
- Poor membrane permeability
- Drug toxicity
- Bad taste
- Short duration of action

Two things are needed to consider when designing prodrugs;

- To ensure that the prodrug is effectively converted to the active drug once it is absorbed into the blood supply.
- To ensure that any groups cleaved from the molecule are non-toxic.

Prodrugs have become an initiated idea and a strong tool in developing the pharmacologically potent structures and get the better of pharmaceutical, physiological and biopharmaceutical barriers to a drug’s functionality.

- Barrier linked to the physicochemical properties of drug
- Barrier in the pharmacokinetic phase.

The poor drug effects such as toxicity, stability, permeability, solubility, drug targeting are genuine challenges for the fortunate growth and commercialization of drug molecules, this can be attain through physical, chemical or biological ways. The biological approach is to alter route of administration which may or may not be allowable to patient. The
physical approach is to adjust the plan of dosage form such as controlled delivery of drug. The third and the finest way in increasing drug selectivity while keeping down toxicity, is the chemical approach for design of prodrugs.

- Functional group derivative involved in prodrug approach:-
  - NH2
  - Amine
  - Alcohol
  - COOH
  - Carboxylic acid

**Functional group** compliant to prodrug design:-
Factors should be examined when designing a prodrug:

a) Parent drug-which functional group are manageable to chemical prodrug derivation.

b) Pro moiety-ideally be safe and rapidly excreted from the body.

c) Parent and prodrug-ADME and pharmacokinetic properties need to be comprehensively known.

**Esters as prodrugs of carboxyl, hydroxyl and thiol functionalities;**
- Esters are common most prodrug used, round about 49% of all marketed prodrugs start up by enzymatic hydrolysis.
- Esters mainly used to enhance lipophilicity.
- Passive membrane permeability of water soluble drugs by disguise charged groups such as carboxylic acids and phosphates.
- Readily hydrolyzed by esterase found in blood, liver, and other organs including, carboxyl esterase, acetylcholinesterase, butyrylcholinesterases.

**Carbonates and Carbamates as prodrugs of carboxyl, hydroxyl or amine functionalities;**
- These are different from esters by the existence of an oxygen or nitrogen of carboxyl carbon on both sides .
- These more stable than esters but more susceptible to hydrolysis than amides.
- Carbonates are derivative of carboxylic acid and alcohols, and carbamates are carboxylic acid and amine derivatives.
- Bioconversions of many carbonate and carbamates prodrugs require.

**Amides as prodrugs of carboxylic acids and amines;**
- In prodrug design, amides been used only to limited range owing to their relatively high enzymatic stability in vivo. Carboxylesterases, peptidases or proteases usually hydrolyses amide bond.
Oximes as derivatives of ketones, amidines and guanidines:

Oximes (for example, guanidoximes, ketoximes, amidoximes) are derivatives of guanidines, ketones, and amidines, thus providing a chance to modify molecules that lack of carboxyl, hydroxyl, or amine functionalities.

- We tabulated a table to summarize, how metabolic consideration is helpful in prodrug approach.

<table>
<thead>
<tr>
<th>PROBLEMS</th>
<th>PARENT DRUG</th>
<th>PRODRUG</th>
<th>How it is solving the problem</th>
<th>Therapeutic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Irritation</td>
<td>Salicylic Acid</td>
<td>Aspirin</td>
<td>increased stimulation of acid secretion or by interference With protective mucosal layer.</td>
<td>Reducing fever, relieve mild to moderate pain.</td>
</tr>
<tr>
<td>Odour</td>
<td>Ethyl mercaptan</td>
<td>Phthalate ester</td>
<td>ethyl mercaptan is foul smelling liquid at BP(35 degree celsius) is converted into its phthalate ester (high BP &amp; odorless)</td>
<td>treatment of Laproxy</td>
</tr>
<tr>
<td>Taste</td>
<td>Chloramphenicol</td>
<td>Palmitate ester</td>
<td>two approaches; a) reduction of drug solubility in saliva b) lower the affinity of drug towards taste receptor</td>
<td>antibiotic (mainly eye infections)</td>
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<td>Bacterial infections</td>
</tr>
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<td>Physical form of drug</td>
<td>Ethyl mercaptan</td>
<td>1,3-diester</td>
<td>ethyl mercaptan is liquid drug and converting of such liquid drug in solid prodrug involves formation of symmetrical molecule having higher tendency to crystallize.</td>
<td>manufacturing of fungicides and bacteriocides</td>
</tr>
<tr>
<td>Low aqueous solubility</td>
<td>Dexamethasone</td>
<td>Hemisuccinates and phosphates</td>
<td>Dexamethasone, because of their low water solubility generally administered in the form of water soluble esters as hemisuccinates and phosphates.</td>
<td>used at higher doses for emergency treatment or other life threatening situations.</td>
</tr>
<tr>
<td></td>
<td>Mitomycin</td>
<td>Tetrandrine</td>
<td>Mitomycin poor solubility in water and in most pharmaceutically acceptable solvents. Prodrug was designed so that mitomycin would be release in vivo by the loss of two molecules of phenylalamin and formaldehyde. Observed that in vitro formaldehyde exerts a catalytic effect on tetrandrine hydrolysis.</td>
<td>Anti - tumor agent</td>
</tr>
<tr>
<td></td>
<td>Azacitidine</td>
<td>Bisulfite produg</td>
<td>The aqueous solution of azacitidine is readily hydrolyzed but bisulfite produg is stable to such as degradation at acidic pH &amp; more water soluble than parent drug. The produg converts to the active drug at the physiological pH of 7.4</td>
<td>Anti-neoplastic agent</td>
</tr>
</tbody>
</table>
CONCLUSION

The present review is a try to collect and confront available information on the subject. Some basic problems, however, been left untouched. For example, for extrapolation of data the difficulty from animals to humans come across during toxicologic and toxicokinetic studies with drugs is added with prodrugs because not only might the metabolism difference of the active moiety, but also its availability from the prodrug. As a matter of fact, there is currently no published rationale for the management of animal and human pharmacokinetic programs during development and prodrug research. Although the prodrug point of view is advancing and reaching successes in providing effective medications to a variety of diseases it still needs the utilization of the sophisticated computational methods used for the design of drugs. Kinetics and thermodynamics for biological systems (active sites of receptors and enzymes, and etc.) that have biomedicinal interests have been intensively researched and have been proved to be fruitful. Today, quantum mechanics, such as ab initio, semi-empirical, and density functional theory (DFT), and molecular mechanics (MM) including docking are increasingly being utilized to characterize active sites of receptors and enzymes. These widely used methods have proven as successful tools for providing structure-energy calculations for an accurate prediction of potential drugs. This plan might help substances too toxic, or impotent to show adequate pharmacologic effects in their basal form to go through primary and secondary screening, before successfully reaching human testing. It is evident that if such an approach were to become an integral part of basic drug design and not just a hindsight attempt to solve problems associated with older drugs, it would also be necessary to develop new biopharmaceutical and pharmacokinetic approaches to tackle the new challenges.

REFERENCES: