Promoieties Used In Prodrug Design: A Review

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ABSTRACT

Despite the success of various prodrugs, surprisingly no other reviews except a review on amino acids as promoieties, which elaborates about amino acids as prodrugs have been published to date. Therefore, we hope that this timely review using both marketed and investigational prodrugs as examples will be of interest for scientists working in the area of drug discovery and development as well as those working in the clinic. In the present commentary we have tried to summarize the different types of promoieties available for prodrug design. The examples of prodrugs using several promoeity are discussed with their advantages and future prospects. The properties and selection of promoieties for the prodrug design is a very crucial parameter in successful prodrug design.

Keywords: Promoeity, prodrug, mutual prodrug, amino acid.

INTRODUCTION

Therapeutic efficacy of a drug can be improved by minimizing or eliminating the unwanted properties while retaining the desirable ones with the approach of drug design. The designing of Prodrugs has given success to overcome the undesirable properties associated with existing drugs.[1] The objective of this review is to help a researcher find out which promoieties would be suitable for prodrug research and what benefits they can offer.[2] Adrien Albert first introduced the term "pro-drug" in 1958. A few decades later, he apologized for having invented such an inaccurate term, because "predrug" would have been a more descriptive term. However, by that time, the original version was used too widely to be changed. The simplest definition of a prodrug was given by Albert as "Prodrugs are chemicals with little or no pharmacological activity, undergoing biotransformation of a therapeutically active metabolite". To synthesize a prodrug, which exhibits better physical properties, is better and a cost effective approach than to synthesize an analogue with a better physical properties.[3] Prodrugs usually improve a drug's physicochemical properties so as to increase the drug concentration at the active site, prolong the effect, decrease toxicity and undesirable side effects. The prodrug should be stable in stomach and in small intestine, non toxic, biodegradable and biocompatible.[4] Prodrug design comprises an area of drug research that is concerned with the optimization of drug delivery.[5]

Drug metabolism is an inevitable process (Figure 1) so in prodrug design a metabolically labile group is added to the drug. The complete opposite of Prodrugs are drugs that have no active metabolite eg paracetamol. It is also necessary to distinguish Prodrugs from soft drugs which are " biologically active compounds characterized by predictable and fast in vivo metabolism

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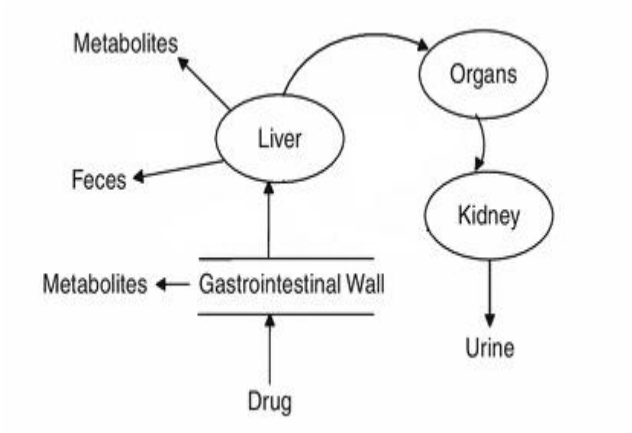

Figure 1: Drug Life cycle and its metabolism

to inactive and non toxic moieties after their therapeutic role eg: esmolol.[2] It has been generally suggested that esterases and proteases are involved in activation in prodrugs, but the enzymes involved are rarely characterized. Activation of prodrugs can be influenced by both promoeity and the drug itself, but very limited studies evaluating the influence of promoeity on the rate of hydrolysis or activation of prodrugs are available. An understanding of the influence of structural parameters of the promoeity on the rate of prodrug activation would therefore facilitate the design of prodrug with optimum stability and activation profiles.[6] Drug pharmacokinetics is dictated by its physicochemical properties which can be altered as desired by selecting a suitable promoeity. Prodrug research is mainly aimed at converting a drug candidate with the desired physico-chemical properties into a form which can be bioactivated. It is estimated that about 10% of the drugs approved worldwide can be classified as Prodrugs, Prodrug design thus comprises an area of drug research that is concerned with optimization of drug delivery.

There are three basic, overlapping objectives in prodrug research:

1. Pharmaceutical: to improve solubility, chemical stability, and organoleptic properties
2. Pharmacokinetic: to improve absorption, to decrease presystemic metabolism, to improve pharmacokinetic profile.
3. Pharmacodynamic: to decrease toxicity and improve therapeutic index, to design single chemical entities combining two drugs.[7]

Types of Prodrugs

Bioprecursor This is obtained by chemical modification of active drugs but does not contain a carrier. Bioprecursor needs activation in vivo to give active species. eg Sulindac.[2]

Macromolecular Prodrugs These have macromolecules like polyethylene glycol, cyclodextrin, chondroitin sulphate as carriers. Proteins, synthetic polymers and polysaccharides are the macromolecules used in drug delivery systems. Macromolecular Prodrugs/Polymeric Prodrugs consist of drug covalently attached to polymeric backbone eg Naproxen Polymeric Prodrug.[2]

Carrier Linked Prodrugs These are Prodrugs where active drug is covalently bonded to a carrier which is usually lipophilic in nature. The active drug is released by hydrolytic cleavage, either enzymatically or chemically.

Mutual prodrugs Here two active agents are combined to give (prodrug) which separates in the body. The mutual prodrug concept is one step ahead as it minimizes side effects along with increase/addition in activity.[1] eg: Naproxen-paracetamol mutual prodrug.[5]

Bioconjugates: These are prodrugs where the carrier is an antibody raised against tumor cells[2]. Antibody conjugated delivery systems e.g. monoclonal antibodies (Mab), which are directed against tumor antigens may be used to target anticancer drugs to target cells for selective killing, mainly these antibodies are "magic bullet" and lead to the formation of immunoconjugates. Immunoconjugates can be Antibody-antibody, Antibody-enzyme conjugates, toxins (immunoconjugates) and chemotherapeutic agents (drug conjugates).

Types of Promoeities

A wide variety of promoieties (Figure 2) have been used to overcome liabilities associated with drugs. The selection of promoeity depends on the purpose of the prodrug, type of functional groups available on the parent drug, chemical and enzymatic conversion mechanisms of prodrug to parent drug, safety of the promoeity, and ease of manufacturing.[8] Several chemical classes of prodrug can be obtained based on functional groups available in drug and promoeity used (Table 1).

Amino Acids

Following features make amino acids useful for conjugation with drugs[9].

1. They are normal dietary constituents and are non toxic in moderate doses.
2. They have gastroprotective action.
3. Large structural diversity and the physicochemical properties of drug can be changed based on nature of amino acid selected for conjugation.
4. Drug targeting can be achieved by proper selection of amino acid.
5. Few amino acids have intrinsic anti-inflammatory activity.
6. Well established prodrug chemistry.
7. Commercial availability.

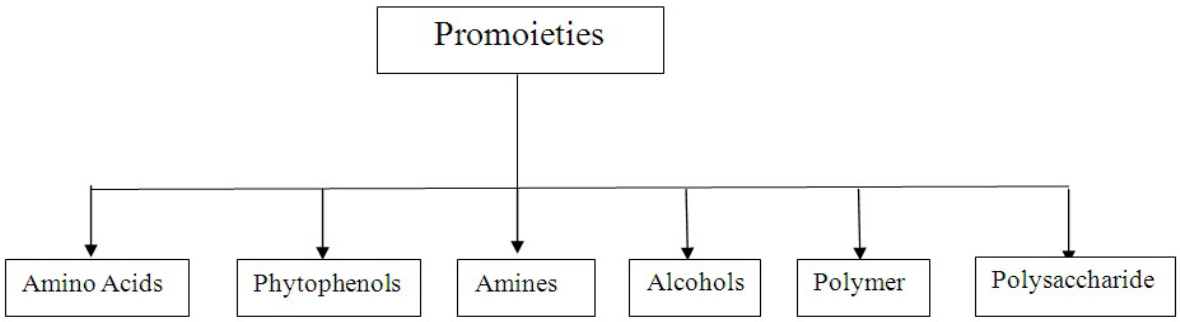

Figure 2: Types of promoieties used in prodrug design

Table 1. Chemical Classes of prodrugs.

Sr no.	Functional Groups	Prodrug Chemical Class
01	Carboxylic(-COOH)	Simple Esters, Acyloxyalkyl esters, Amides, Phosphoxyalkyl esters
02	Hydroxyl Group(-OH)	Simple esters, Acyloxyalkyl esters, Carbamates, Carbonates, Phosphoxyalkyl esters, Phosphate esters.
03	Sulfhydril (-SH)	Thioesters, Acyloxyalkyl thioesters, Disulphides.
04	Amine (-NH2)	Amides, Carbamates, Imines, Enamines
05	Carbonyl	Oximes, Imines, Enamines, Acetals, Hydrazones

Good pharmacological response for amino acid Prodrugs indicates that absorption of Prodrugs might be regulated by some other means like presence of amino acid transport system besides dissolution.[9] Amino acid contains both acidic and basic groups in the same molecule and exists in zwitterionic form. The non availability of free amino group in zwitterionic form of the amino acid restricts its use in formation of amidic Prodrugs. So amino acid ester hydrochlorides are used in which the neutralization of HCl using base generates free amino group to react as nucleophile in synthesis of amide prodrug.[10]

By proper selection of amino acid (Table 2), the polarity, solubility profile and acid base properties of a given drug molecule can be altered completely.[11]

Polymers

The conjugation of a biologically active compound with a polymer is one of the many methods for altering and controlling the pharmacokinetics, biodistribution and often toxicity of various drugs.[14] The task of obtaining a versatile polymer as an ideal candidate in drug delivery can be intricate since it has to surmount several vigorous clinical barriers.[15]

Polyethylene glycols (PEGs) appear to be particularly convenient as oligomeric matrices, since they are easily available in wide range of well definite molecular weights. PEGs are well known to be non toxic, non antigenic and biocompatible. Given these properties, it is fantastic for use as a drug carrier as it is also rapidly eliminated from body.[3]

Table 2. Amino acid prodrugs[2,6,9,10,11,12,13]

Sr no.	Amino Acid	Drug	Advantage
01	Glycine, Phenyialanine, Tryptophan, L-valine, L-isoleucine, L-alanine, L-leucine, L- glutamic acid, L-aspartic acid and β-alanine	Ketorolac	Controlled release and decreased gastrointestinal side effects
02	Alanine and Histidine	Aceclofenac	Less Gastrointestinal Side Effects
03	L- tryptophan, L- Histidine, L-phenylalanine, DL-alanine	Flurbiprofen	Decreased gastrointestinal side effects
04	Phenylalanine, valine and proline	Floxuridine	Good Solution Stability and Fast Enzymatic Conversion Rates
05	Glycine, alanine, leucine, lysine, phenylalanine	Dapsone	Improved water solubility
06	Valine	Saquinavir, Indinavir and Nelfinavir	Improved pharmacological and pharmacokinetic profile
07	Glycine, Cysteine, tryptophan, lysine and phenylalanine	Cinmetacin	Reduced Gastrointestinal side effects

PEG is a polymer that holds many interesting applications in a wide range of biotechnological and pharmacological fields due to its unique chemical and biological properties.

Most important feature of polyethylene glycol modification is that it greatly extends the half life of most proteins and drugs. Polymeric prodrugs of several drugs have been synthesized and evaluated (Table 3).

Polysachharides

NSAIDs conjugated with polysaccharide specifically for colon targeting have been studied with cyclodextrin, dextran, pectin, chitosan and chondroitin (Table 4). Chondroitin sulphate, a co polymer of D-glucoronic acid and sulphated N acetyl D-galactosamine, is an important structural component in connective tissue and cartilage. It can be used as a good candidate for colon targeted drug carriers. Cyclodextrins (CDs) belong to the family of oligosaccharides. They are obtained by enzymatic degradation of starch. CDs are nontoxic and thought to be one of the most suitable promoieties to reduce ulcerogenic tendency of drugs. Dextran has excellent physicochemical properties, physiological response and unique pharmacokinetic profile. The literature reveals that in most polymeric prodrugs, the drug is linked to polymeric carrier by a chemical linkage.[15] Dextran was investigated as a macromolecular carrier for delivering drugs and also demonstrated that it is useful to target therapeutic agents to the liver.[23]

Alcohols

Esters have dominated research because; they have ideal characteristics, exhibiting (reasonable) sufficient chemical stability in vitro and their ability to function as esterase substrates for in vivo regeneration[27].

Cyclohexanol, cyclopentyl alcohol, isobutyl alcohol, t-butyl alcohol (Table 5) are alcohols used as promoieties in synthesis of ester prodrugs. Iodomethyl pivalate and 2- Bromo ethyl acetate are also used.

Phytophenols

Phytophenols are used traditionally for their medicinal as well as flavoring properties, with well documented safety profiles. Phytophenols are used as carriers for prodrugs in an attempt to combine anti-inflammatory and antioxidant properties.[30] Naturally occurring phenolic antioxidants are thymol, guiacol and eugenol whereas menthol is alcoholic compound.

Menthol, Thymol, Eugenol, Guiacol, vanillin, umbelliferone (Table 6) are the Promoieties used in prodrug

Table 3. Polymeric Prodrugs[1,3,14,16,17,18,19,20,21,22]

Sr no.	Polymer	Drug	Advantage
01	Polyethylene glycol	Theophylline	Improved biopharmaceutical properties
02	Polyethylene glycol	Ketoprofen	Extended Pharmacological Effect Owing to Delayed-Release of Parent Drug
03	2- hydroxyl methyl acrylate	Naproxen	Enhanced Potency and longer duration of action
04	Polyethylene glycol 2000	Warfarin	Improved biopharmaceutical properties
05	Polyethylene glycol 5000, 10000	Metronidazole	Improved Pharmacokinetic Properties
06	polyethylene glycol esters	Methotrexate	Improved stability and drug delivery
07	Polyethylene glycol	Ibuprofen	Extended duration of action
08	Polyethylene glycol	Theophylline	Good Release of Parent Drug
09	Polyethylene glycol	Mesalazine	Colon specific drug delivery
10	Acrylate polymeric prodrug	Ibuprofen	Increased Antiinflammatory Activity

Table 4. Polysaccharide Prodrugs[4,14,15,23,24,25,26]

Sr no.	Polysaccharide	Drug	Advantage
01	Chondroitin sulphate	Ibuprofen, ketoprofen, naproxen	Synergistic anti-inflammatory effect and delayed release of drug
02	Cyclodextrin	Mefenamic acid	Mask the Ulcerogenic Potential of Free carboxylic group
03	Chitosan glucosamine	Metronidazole	Colon Targeted Drug Delivery System
04	Dextran	Flurbiprofen and suprofen	Improved Analgesic and Antipyretic Activities with Low Ulcerogenic Indices
05	Chitosan conjugates	Metronidazole	Colon Targeted drug delivery
06	Dextran conjugates	Valproic acid	Reduction in Hepatotoxicity and Ulcerogenicity
07	Dextran conjugates	Acyclovir	Targeting of antiviral drug to liver
08	Dextran	Metaxaolne	Improved Pharmacokinetics and longer Half Life

Table 5. Ester Prodrugs[28,29]

Sr no.	Alcohol	Drug	Advantage
01	Cyclohexanol, cyclopentyl alcohol, isobutyl alcohol, t-butyl alcohol	Flurbiprofen	Reduced Gastrointestinal Side Effects
02	Iodomethyl pivalate, 2- bromo ethyl acetate	Indomethacin	Decreased Gastrointestinal Side Effects

Table 6. Phytophenolic Prodrugs[1,30,31,32]

Sr no.	Phytophenol	Drug	Advantage
01	Menthol, Thymol, Eugenol	Ibuprofen	Synergistic analgesic action and Decreased gastrointestinal toxicity.
02	Guiacol, Eugenol, thymol, vanillin, Umbelliferone, menthol	Diclofenac	Reduced Ulcerogenic Side Effects
03	Guiacol	Mefenamic Acid	Synergistic anti-inflammatory activity and less toxicity

synthesis. They offer antioxidant as well as gastroprotective properties.

Amines

Several compounds like propyl–amine, diethylamine, cyclohexyl amine, 2–amino ethyl amine, 2–hydroxyl ethyl amine, Ethylenediamine, benzathine and cysteamine (Table 7) are used as promoieties in synthesis of amide prodrugs. These form amide bonds with carboxylic groups of drug moiety.

Mutual Prodrugs

Mutual Prodrugs (Table 8) involved combining two different pharmacophore with similar pharmacological activities to give synergistic action or different pharmacological activities whose action is needed together.[36]

Conclusion

As depicted, the prodrug design has found a number of compounds in clinical use. Selection of promoeity in prodrug research should be done wisely as it will determine the regeneration of active drug *invivo* and also the promoeity itself should be nontoxic and excreted soon. In case of mutual prodrug, promoeity may even add to therapeutic action. A large number of prodrug examples published in literature indicate that newer advances to clinical practice. Fruitful prodrug design is the task that depends on how prodrug satisfies or achieves pharmacokinetic and pharmacodynamic objectives of drug action.

Table 7. Amide Prodrugs[33,34,35]

Sr no.	Amine	Drug	Advantage
01	Propyl amine, diethylamine, cyclohexyl amine, 2-amino ethyl amine, 2- hydroxyl ethyl amine	Ketoprofen	Reduced Gastrointestinal Side Effects, Improved Analgesic Activity
02	Ethylenediamine and benzathine conjugate	Ibuprofen	Reduced Gastrointestinal Side Effects, Improved Analgesic Activity
03	Heterocyclic Amide	Ibuprofen	Improved Analgesic Activity, Lower Ulcerogenic Activity
04	Amide derivatives	Diclofenac	Lower Ulcerogenic Activity
05	Cysteamine	Ibuprofen and Indomethacin	Antioxidant activity and Lower Ulcerogenic Activity
06	Glycine amides	Ketoprofen	Lower Ulcerogenic Activity

Table 8. Mutual Prodrugs[5,24,36,37,38,39]

Sr no.	Drug	Second drug	Advantage
01	Indomethacin	Paracetamol	To combine antipyretic and anti-inflammatory activity
02	Stavudine	Ciprofloxacin	Combined antibacterial and antiviral activity
03	Ibuprofen	Paracetamol	To combine antipyretic and anti-inflammatory activity
04	Naproxen	Propyphenazone	To combine antipyretic and anti-inflammatory activity
05	Meclofenamic acid	Quercetin	Antioxidant and anti-inflammatory activity
06	Mefenamic Acid	Salicylic acid and Salicylamide	Synergistic analgesic activity and reduced gastric side effects
07	Flurbiprofen	H2 Antagonist	Providing antacid action to prevent GI side effects

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