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PRODRUG APPROACH - A REVIEW

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ABSTRACT

Prodrug design is a choice of approach in solving many of the stability, solubility, permeability and targeting problems that plague drug discovery and development. The prodrug approach has the ability to keep promising new drug candidates alive through development, and improving the safety and efficacy of existing drug products. It is a very fruitful area of research and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs suffering from undesirable side-effects. About 14% of drugs approved worldwide can be classified as prodrugs. The present article takes a review of introduction and applications of prodrug design in various areas of drug development by overcoming side-effects of existing drugs.

Keywords: Prodrug, Carrier, Pro-moiety, Parent drug, Bioprecursor, Mutual Prodrug,

INTRODUCTION

A prodrug can be defined as a drug substance that is inactive in the intended pharmacological actions and is must to be converted into the pharmacologically active agent by metabolic or physico-chemical transformation [1].

Prodrugs can exist naturally such as many phytochemicals/botanical constituents and endogenous substances, or they can result from synthetic or semisynthetic processes – produced intentionally as part of a rational drug design or unintentionally during drug development.

Examples of prodrugs that exist naturally or were produced unintentionally during drug development:

They include aspirin, psilocybin, parathion, irinotecan, codeine, heroin, L-dopa, and various antiviral nucleosides.

Examples of products resulting from pharmaceutical processes as part of strategically targeted drug design:

- sulfasalazine, oseltamivir,
- Various nonsteroidal anti-inflammatory drugs (ketoprofen, diclofenac),
- Statins (lovastatin, simastatin),
- ACE inhibitors (captopril, lisinopril) and
- Penicillin-related agents (bacampicillin, sarmo xicillin).

Need or objectives to design and produce a prodrug

1. Pharmaceutical objectives:

(1) Bioavailability, such as poor aqueous solubility (*e.g.*, corticosteroids),
(2) To improve chemical stability (*e.g.*, short half-life, such as dopamine),
(3) To improve organoleptic properties (chloramphenicol)
(4) To decrease irritation and pain [2]

2. Pharmacokinetic objectives

(1) To improve oral absorption or permeability and thus increase bioavailability (ampicillin, Epinephrine),
(2) To decrease first pass metabolism (propanolol).
(3) To improve absorption by non oral routes.
(4) To provide organ or tissue selective delivery of active agent.

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3. Pharmacodynamics objectives
(1) To avoid adverse effects or toxicities.
(2) To mask reactive species to improve its therapeutic index.
(3) To improve site specificity (*i.e.*, that the site of action of an active drug is rather nonspecific such as anticancer agents).

Principal concerns and specific difficulties during prodrug development
1) Whether the prodrug converts sufficiently fast and completely into the active drug format (in other words how long and how much remains intact in the body)
2) Whether the prodrug contributes significantly to the active drug's toxicity profile (which is especially important when it exhibits unique and different toxicities compared to the converted active drug) [3].

Classification of prodrugs
I. Conventional classification
(1) Based on therapeutic categories
Examples: anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, nonsteroidal anti-inflammatory prodrugs, cardiovascular prodrugs, etc;

(2) Based on the categories of chemical linkages or moiety/carriers that attach to the active drug:
Examples: esteric prodrugs, glycosidic prodrugs, bipartite prodrugs, tripartite prodrugs, and antibody-, gene-, virus-directed enzyme prodrugs;

(3) Based on functional categories using strategic approaches to circumvent deficiencies inherent to the active drug:

Examples: prodrugs for improving site specificity, prodrugs to bypass high first-pass metabolism, prodrugs for improving absorption, and prodrugs for reducing adverse effects [4].

II. Novel classification of prodrugs
Prodrugs are classified in this classification based on their cellular sites of conversion into the final active drug form:-
1. Type I
They are converted intracellularly
e.g. Anti-viral nucleoside analogs, lipid-lowering statins, etc.

2. Type II
They are converted extracellularly, especially in digestive fluids or the systemic circulation
e.g. Etoposide phosphate, valganciclovir, fosamprenavir, antibody directed enzyme prodrugs (ADEP), gene directed enzyme prodrugs (GDEP) or virus-directed enzyme prodrugs (VDEP) for chemotherapy or immunotherapy).

Both types can be further categorized into Subtypes, *i.e.*, Type IA, IB and Type IIA, IIB, and IIC based on whether or not the intracellular converting location is also the site of therapeutic action, or the conversion occurs in the gastrointestinal (GI) fluids or systemic circulation [5].

- Type IA prodrugs include many antimicrobial and chemotherapy agents (*e.g.*, 5-flurouracil).
- Type IB agents rely on metabolic enzymes, especially in hepatic cells, to convert the prodrugs intracellularly to active drugs.
- Type II prodrugs are converted extracelluarly,

i. Either in the milieu of GI fluids (Type IIA),
ii. Within the systemic circulation and/or other extracellular fluid compartments (Type IIB), or
iii. Near therapeutic target tissues/cells (Type IIC), relying on common enzymes such as esterases and phosphatases or target directed enzymes.
iv. Prodrugs can belong to multiple subtypes (i.e., Mixed-Type). A Mixed-Type prodrug is one that is converted at multiple sites, either in parallel or sequential steps.

Example: A prodrug, which is converted concurrently in both target cells and metabolic tissues, could be designated as a "Type IA/IB" prodrug.
(e.g., HMG Co-A reductase inhibitors and some chemotherapy agents; note the symbol "/**"** applied here). When a prodrug is converted sequentially, for example initially in GI fluids then systemically within the target cells, it is designated as a "Type IIA-IA" prodrug (*e.g.*, tenofovir disoproxil fumarate; note the symbol "**-"** applied here). Many ADEPs, VDEPs, GDEPs and futuristic nanoparticle- or nanocarrier-linked drug moieties can understandably be Sequential Mixed-Type prodrugs. To differentiate these two Subtypes, the symbol dash " - " is used to designate and to indicate sequential steps of conversion, and is meant to distinguish from the symbol slash " / " used for the Parallel Mixed-Type prodrugs [6].

Approaches to prodrugs with lipoproteins
1. Prodrugs for treatment of vascular thrombosis
Eg: Ximelagatran ⟶ melagatran
2. Gemcitabine prodrug is delivered by liposomes for improving the antitumour activity and pharmacokinetics.
3. Levo dopa diacetyl ester is delivered by liposomes for the treatment of Parkinsonism disease
4. Anticancer double lipid prodrugs are produced for delivery of phospholipase A2, an enzyme that is upregulated in various cancer cells.
5. Antitumoral activity of liposomes and immunoliposomes containing 5-fluorouridine prodrugs is also used.
6. Liposomal emulsions of mitomycin-C prodrug is used for antitumoural activity.

7. Ultra sound ruptured liposomes for enzyme prodrug therapy are also under research. They are are used in delivery of antitumour drugs [7].

Prodrugs approach with block copolymers

1. Block copolymers of PLA and poly ethylene glycol or poly amino acids have been used to make polymerosomes through which prodrugs are delivered by micells /nanoparticles.

2. Polymeric micelles are also used in delivery of tuberculo static drugs

Eg: By the condensation of hydroxyl methyl pyrazinamide, isoniazid and rifampin with free carboxyl groups on the copolymer poly (ethyleneglycol)-poly (aspartic acid), micelle forming carrier-drug conjugates were obtained

3. Polymer micelles as novel drug carriers used for preparation of adriamycin-conjugated poly(ethylene glycol)- poly(aspartic acid) block copolymer.

4. Doxorubicin is targeted to liver by conjugating with block copolymers like polyamidoamine dendrimer (PAMAM) and Polyethylene glycol [8].

Applications / Purposes

1. Pharmaceutical applications:

- Improvement of taste

Eg: chloramphenicol palmitate is the sparingly soluble of prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubility as well as it is hydrolysed to active chloramphenicol by the action of pancreatic lipase.

- Change in the physical form of drug

Eg: esters of trichloroethanol

Trichloro ethanol ⟶ p-acetamidobenzoic acid ester
(Drug) (prodrug)

- Improvement of odour

Eg: ethyl mercaptan ⟶ phthalate ester
(drug) (prodrug)

- Reduction of gastric irritation

Eg: Aspirin is a prodrug of salicylic acid is designed to reduce gastric irritation

Diethyl stilbesterol ⟶ fosfesterol
Kanamycin ⟶ kanamycine pamoate
Phenyl butazone ⟶ N-methyl piperazine salt
Oleandrin ⟶ oleandrin acetate
Nicotinic acid ⟶ nicotinic acid hydrazide

- Reduction in pain on injection

Eg: IM injection of antibiotics like clindamycin and anti convulsant like phenytoin was found to be painful due to poor solubility. So, prodrugs are produced like 2'phosphate ester of clindamycin and hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin respectively.

- Enhancement of drug solubility and dissolution rate

Eg: chloramphenicol ⟶ chloramphenicol palmitate
Chloramphenicol ⟶ chloramphenicol succinate
Sulindac ⟶ sulindac sulphate
Testosterone ⟶ testosterone phosphate ester
Tetracycline ⟶ tetralysine
Diazepam ⟶ diazepam L-lysine ester

- Enhancement of chemical stability

Eg: vaccines, cytotoxic agents, antibiotics like ampicillin.

2. Pharmacokinetic applications:

- Enhancement of bioavailability

Eg: a. oral bioavailability
Dopamine (drug) ⟶ L-dopa(prodrug)
b. ophthalmic bioavailability
epinephrine ⟶ dipivalyl derivative
c. percutaneous bioavailability
Mefenide ⟶ mefenide hydrochloride/acetate

- Prevention of presystemic metabolism

Eg: Dopamine (drug) ⟶ L-dopa(prodrug)
Terbutaline ⟶ Ibuterol
Morphine ⟶ diacetyl morphine
N-(t-butyl arternol) ⟶ bitoterol

- Prolongation of duration of action

Eg: pilocarpine in treatment of glaucoma
Fluphenazine (neuroleptic drug) ⟶ heptanoate, decanoate esters In sesame oil
Testosterone ⟶ 17β-propionate ester, 17-phenyl acetylate ester or 17-cypionate ester in oil
propanolol ⟶ hemisuccinate prodrug

- Reduction of toxicity

Eg: toxicity of sulindac sulphide, 5,5-ethyl phenyl hydrazine, phenytoin, adriamycin due to inadequate aqueous solubility, improper distribution and high tissue distribution respectively is reduced by prodrugs.

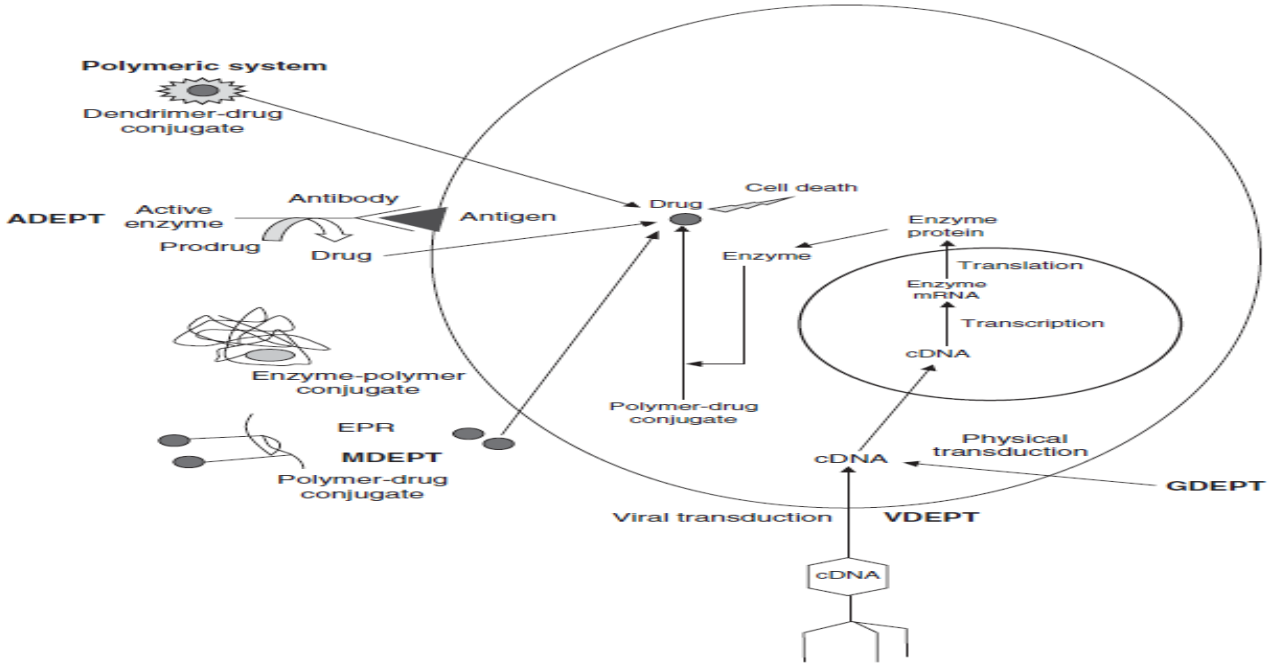
- Site specific delivery

Eg: antibody directed enzyme prodrug therapy,
Gene directed enzyme prodrug therapy, etc

Acyclovir ⟶ acyclovir monophosphate ⟶ (cellular kinase) acyclovir triphosphate

⇓

Viral DNA



Prodrug Types	Site of Conversion	Subtypes	Tissue Location of Conversion	Examples
Type I	Intracellular	A	Therapeutic Target Tissues/Cells	**Type IA:** Acyclovir 5-Flurouracil Cyclophosphamide Diethlstilbestrol diphosphate L-Dopa 6-Mercaptopurine Mitomycine C Zidovudine
		B	Metabolic Tissues (liver, GI mucosal cell, lung, etc.)	**Type IB:** Cabamazepine Captopril Carisoprodol Heroin Molsidomine Paliperidone Phenacetin Primidone Psilocybin Suldinac Tetrahydrofurfuryl disulfide
Type II	Extracellular	A	GI Fluids	**Type IIA:** Lisdexamfetamine Loperamide oxide Oxyphenisatin Sulfasalazine
		B	Systemic Circulation and Other Extracellular Fluid Compartments	**Type IIB:** Acetylsalicylate Bacampicillin Bambuterol Chloramphenicol succinate Dihydropyridine pralixoxime Dipivefrin Fosphenytoin
		C	Therapeutic Target Tissues/Cells	**Type IIC:** ADEPs GDEPs VDEPs

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