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Cutting Edge Approach on Prodrug: Contrivance for Target Drug Delivery

Y M Varsha[1]*, G Ram Mohan Rao[2] and V Venkateswara Rao[1]

[1]*School of Chemical and Biotechnology, SASTRA University, Tamil Nadu, India
[2]School of Bio-Engineering, SRM University, Tamil Nadu, India

Abstract

Drug administration procedures are very much vital and are considered to be the prime-most criteria during the drug design and its appliance. Scrutinizing this, drugs are designed in such a way, bringing some change in their persona like bioavailability and bioequivalence. One such approach called prodrug, first started in 1950's is still a fertile area of research because of it's insist persona. Prodrugs are the shrouded drugs which are one or two chemical or enzymatic steps away from the active parent drug. Present review delineates about the prodrug action, types of prodrugs, new prodrug therapies, nanotech allied prodrugs.

Keywords: Prodrug; Bioequivalence; Pro-prodrug; Mutual prodrug; Nanoparticles

Abbreviations: 5-ASA: 5-Amino Salicylic Acid; AZT: Azidothymidine; ADC: Antibody-directed catalysis; ADEPT: Antibody-directed enzyme prodrug therapy; GDEPT: Gene-directed enzyme prodrug therapy; VDEPT: Virus-directed enzyme prodrug therapy; PDEPT: Polymer-Directed Enzyme Prodrug Therapy; LEAPT: Lectin-directed enzyme-activated prodrug therapy; CDEPT: Clostridial-directed enzyme prodrug therapy; MSN:Mesoporous silica nanoparticles; GNP: gold nanoparticles; SNP: silver nanoparticles; SLM: Solid Lipid Microparticles.

Introduction

A drug is a small organic molecule introduced in to the body for cure, prevention, treatment or diagnosis of disease or else used to improve mental and physical well-being. This generally binds to the specific site or organ /cell and activates or inhibits the function of the desired biomolecule [1]. When a drug is injected/ swallowed/inhaled, they find their way into the bloodstream and are transported to different parts of the body, finally reaching the targeted cell/tissue. Drug may be obliging or damaging, which depends on the kind of drug taken, how much is taken, how often it is used, how quickly it reaches the target, and what other drugs, food, or substances are taken at the same time. Drug administration is associated with certain problems like biodistribution of pharmaceuticals throughout the body, undesirable side-effects due to high drug doses, lack of drug specific affinity toward a pathological site, need of a large total dose of a drug to achieve high local concentration; non-specific toxicity etc. [2,3]. Like such, several challenges are unmet and there is a need of new techniques for drug developments and their application [4].

Pharmacotherapists and other concerned researchers have made their efforts to reduce the frequency of the dosages taken by the patient, drug side effects, and fluctuation in circulating drug levels by introducing targeted drug delivery system [5-8], which have a protected drug interaction with the diseased tissue. Although seemed to be a costlier process, shows a prolonged, localized effect on the specific targeted cell/tissue [9]. Chemical eradication of undesirable properties of the drug (low oral absorption properties, bad taste, odor etc) is done mainly by designing and developing the drug in the favored approach. Moreover bioequivalence and bioavailability studies are considered as important measures, so that the designed drug can be applied in a right way [10-12]. Keeping all these in mind, one such amendment which came in to existence is the Prodrug, defined to be chemically modified inert drug precursor which can be biotransformed in to active parental molecule. Prodrug is considered as an innovative and very interesting strategy bringing adaptation in the drug delivery process by improving the bioavailability of various drugs like Docarpamine, Etilevodopa, Xeloda etc. [13].

Prodrug Notion

Prodrug or proagent is the masked form of active drug, introduced by Albert and et al. in 1950s, to increase the efficiency of drugs and to decrease its associated toxicity. Though given many names like latentiated drugs (since the concept was discussed in late 1950s), bioreversible derivatives, congeners, prodrugs suits a lot and is commonly accepted term [14]. Appropriate exploit of Prodrugs was only since the late 19th century, which mainly focused to improve undesirable properties of drugs [15]. Prodrugs can be defined as pharmacologically inert chemical derivatives that can be transformed in vivo to the active drug molecules, enzymatically or nonenzymatically, to wield a therapeutic effect [16,17].

As shown in Figure 1, prodrug is considered to be the combination of active drug and side chain/ligand (covalently linked) which helps in targeting the specific cell/tissue. Prodrug is converted to the original drug once it reaches the site of action, followed by rapid abolition of the released derivatizing group without causing side effects.

Persona of an imperative prodrug

An ideal prodrug should have the following characteristics so as to be released in the pharma market [18,19]

- Readily transported to the site of action (active or passive transport across biological barrier)
- Rapid transformation in to active form (Must be selectively

***Corresponding author:** Y.M. Varsha, School of Chemical and Biotechnology, SASTRA University, India, E-mail: varsha_ym@yahoo.com

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cleaved to the active drug utilizing special enzymatic profile of the site)

- Once the prodrug is selectively generated at the site of action, the tissue must retain the active drug without further degradation
- Release non-toxic metabolic fragments after its transformation with rapid elimination

Prodrug: Categorization

Figure 2 elucidates about the classification of prodrugs based on cellular site of bioactivation and methods of bioactivation. Bioactivation of drugs may be intracellular or extracellular. Hepatic cells, liver cells etc. relay on metabolic enzymes for Prodrug to be converted to active drug intracellularly. Carbamazepine (anticonvulsant used for treatment of bipolar disorder), Captopril (ACE inhibitors used to treat some types of congestive heart failure), Psilocybin (naturally occurring Prodrug produced by small mushrooms like *Psilocybe cubensis, P. semilanceata* etc). While some antimicrobial and chemotherapy agents like Procytox, Purinethol (immunosuppressive drug), azidothymidine (AZT, a class of antiretroviral drug acting on HIV) intracellularly acts directly on the specific tissue/cell. Extracellular bioactivation may occur in gastrointestinal fluids or in other extracellular fluids. Common

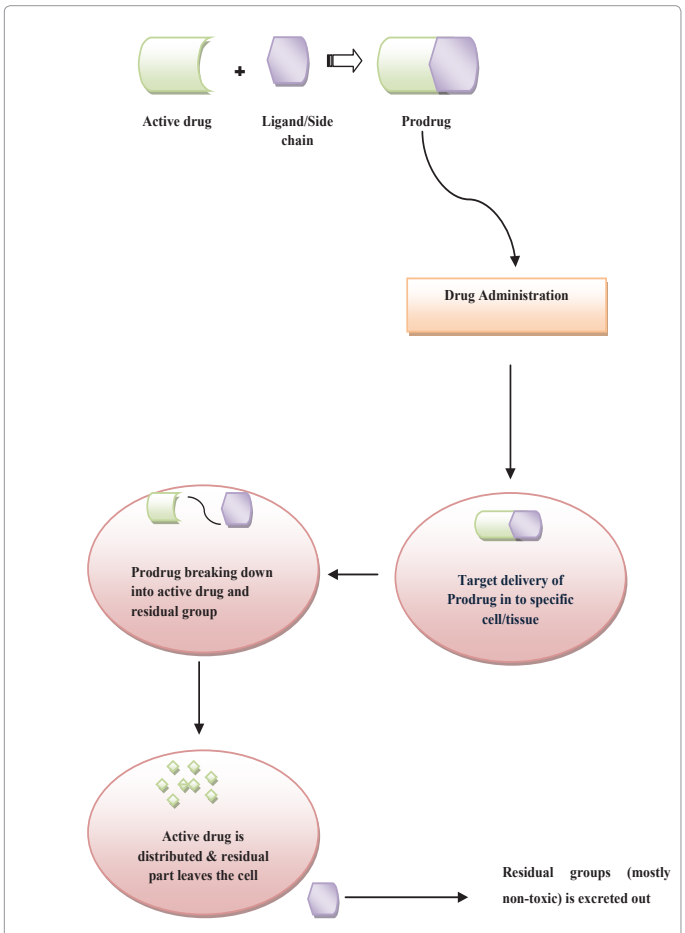

Figure 1: Prodrug action on targeted cells

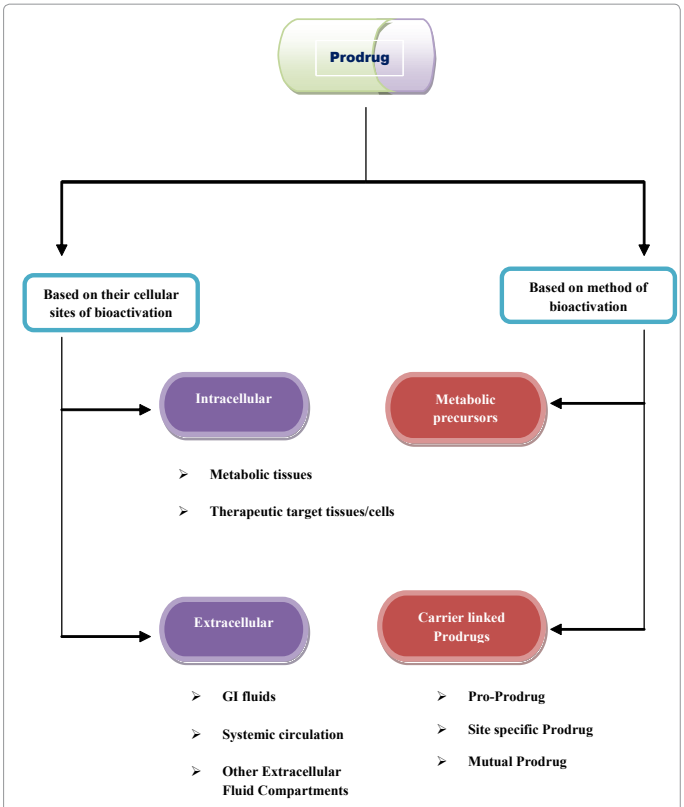

Figure 2: Classification of prodrugs.

prodrugs which tracks extracellular bioactivation are Chloramphenicol succinate, Bacampicillin (penicillin antibiotic), Dipivefrine (used to treat glaucoma), Azulfidine (used to treat rheumatoid arthritis) etc. [20].

A Prodrug is mainly designed to attain smooth and apposite bioactivation. Based on the method of bioactivation the system or the body needs, prodrugs are equipped with some metabolic precursors or any ligands/carriers. Prodrugs with bioprecursors are due to some simple chemical modifications like redox reactions, while Prodrug carrying a ligand or any inert carrier like ester, amide, phosphate [21] can be alienated in to Pro-prodrug, Site specific Prodrug, Mutual Prodrug.

- Pro-prodrug, also called as double prodrug formed by the technique called cascade latentiation is made of two side chain or ligand derivatives (unstable bonds), mostly ester molecules where the first ester is cleaved enzymatically and the second one under goes non-enzymatic/chemical hydrolysis [22]. Roberta et al reported L-Lysine Pro-Prodrug Containing trans-Ferulic Acid for 5-Amino Salicylic Acid (5-ASA) Colon delivery, to treat Crohn disease [23].
- Site specific Prodrug functions mainly as transporter of the active drug which targets to the desired or specific tissue/cell. Most of the prodrugs are designed to target the specific cell which is contented by this type of Prodrug. Antibody-directed catalysis (ADC) consisting of F(ab')-β-lactamase conjugates and a cephalosporin derivative of the oncolytic agent 4-desacetylvinblastine-3-carboxhydrazide are best apposite example for the site specific prodrugs [24].

- Mutual Prodrug incorporates two pharmacologically active agents, each acting as promoiety for the other agent. In this the carrier molecule is a drug which helps in overcoming side effects caused by the parent active drug, improving site specificity etc. The best example of mixed drug is Paracodol, a generic pain killer which is thecombination of paracetamol and codeine [25].

Prodrug Therapy

The prodrug design includes an unfixed position that can be altered to improve in membrane permeability, solubility or absorption, distribution, metabolism, and elimination (ADME) properties. Different Prodrug/ enzyme systems used for cancer therapies and other related therapies includes

- Antibody-directed enzyme prodrug therapy
- Gene-directed enzyme prodrug therapy
- Virus-directed enzyme prodrug therapy
- Polymer-Directed Enzyme Prodrug Therapy
- Lectin-directed enzyme-activated prodrug therapy
- Clostridial-directed enzyme prodrug therapy

Antibody-Directed enzyme prodrug therapy (ADEPT)

In this targeted therapy, tumor-specific antibody-enzyme conjugate is administered followed by a non-toxic prodrug after a specific time interval [26]. The antibody-enzyme conjugate will help in selective binding of enzyme to the tumor cell and then the prodrug converts in to active drug (toxic) by this targeted enzyme, thus only affecting the tumor and leaving back the normal cells. This idea of using antibodies to carry a specific enzyme to the tumor was explored by Philpott et al. [27]. The first clinical trial of this is done using benzoic acid mustard L-glutamate, which is cleaved by carboxypeptides G2 to give L-glutamic acid and the more toxic nitrogen mustard derivative of benzoic acid [28].

Gene-Directed enzyme prodrug therapy (GDEPT)

GDEPT, also known as suicide gene therapy is a similar targeted technique where the gene for foreign enzyme is delivered (mostly by Liposomal or polymer mediated gene delivery) [29-35] to the tumor cell which further activates the non toxic prodrug at the site of action [35]. Here the genes are controlled at transcription site by using specific promoter that becomes active in target cells transcribing to mRNA which further translates in to protein. GDEPT genes are isolated from different bacteria, yeast, plants, and viruses. The best studied system which is under the clinical trials is herpes virus thymidine kinase (TK), used with the cold-sore drug ganciclovir (GCV), which is converted to a DNA synthesis inhibitor that is only active in dividing cells [37]. Many genetic modifications and mutations can be done to bring up this technique in effortless way. In certain cases, it is alleged that a single dose of this GDEPT gene will aid in bringing change in the tumor count.

Virus-Directed enzyme prodrug therapy (VDEPT)

In this pharmacologically oriented gene therapy, viral vector encoding the prodrug-activating enzyme are used followed by efficient treatment with prodrug to attain high levels of activated cytotoxic at the proposed site of action. VDEPT has three possible resource of toxicity: vector, prodrug, and the vector/prodrug combination. It has been reported that, a VDEPT approach using the gene suicide system NTR/CB1954 (*E. coli* nitroreductase enzyme/ prodrug CB1954) combination appears promising for the treatment of cancer metastatic to the liver and the peritoneum [38]. Many such different viral, plasmid, retroviral, adenoviral vectors are used nowadays for this target delivery process.

Polymer-Directed enzyme prodrug therapy (PDEPT)

A novel two step antitumor approach where the polymeric prodrug is administered, first promoting tumor targeting and later activating polymer-enzyme conjugate (PEG-L-asparginase). Here the polymer enzyme conjugates are used as drug carrier or linker, used as anticancer agent [39]. This strategy is presently under phase I/II which includes conjugates like N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer–doxorubicin (PK1, FCE28068), HPMA copolymer–paclitaxel (PNU 166945) etc. [40,41]. A recent technique involving the same technique is polymer-enzyme liposome therapy (PELT) that can cause explosive release of drug from either polymeric prodrugs or liposomes within the tumor interstitium. Another novel technology, microsphere carrier systems made from biodegradable polymers, having bioadhesive property is coming in to picture dealing with the disease Myasthenia Gravis [42].

Lectin-Directed enzyme-Activated prodrug therapy (LEAPT)

LEAPT is a biparticle drug delivery system that exploits endogenous carbohydrate-to-lectin binding to localize glycosylated enzyme which determines site of drug release and a capped prodrug released by that enzyme [43]. Since this is a new emerging technique, only little information has been shared regarding this and more have to be explored yet.

Clostridial-Directed enzyme prodrug therapy (CDEPT)

A fact of tumor-targeting properties of nonpathogenic strains of *Clostridia* and spores which are incapable of germinating in healthy tissue made researchers to bring this novel technique called Clostridial-directed enzyme prodrug therapy [44]. This came in to existence when Minton et al declared that therapeutic proteins delivered using clostridial spores have been prodrug converting enzymes [45]. Specific reports on nitroreductase (NTR) class which converts the 4-nitrogroup of the prodrug CB1954 (5-aziridinyl-2,4-dinitrobenzamide) to toxic 4-hydroxylamine (4HX) derivative (apoptosis-inducing agent) bought evidence to bring up this efficient therapy to treat many cancers [46].

Prodrug as a Part of Nanoworld

Researchers are now indulged to apply nanotechnology in designing the prodrugs for better delivery of drugs to the targeted site (targeting being an publicized promise of nanotechnology) [47-49], to increase its reactivity, to increase its surface-volume ratio [50,51], to reduce the toxicity (for good safety and biocompatibility) [52] and also to retain their lifespan till it reaches the site of action [53-58].

Mesoporous silica nanoparticles (MSN) [59,60], gold nanoparticles (GNP) [61,62], silver nanoparticles (SNP) [63-65], Solid Lipid Microparticles (SLM) [66,67] etc are used as nanocarriers/polymeric nanoparticles [68,69], nanoshells (concentric particle coated with thin layer of inert coat) [70], which will protect the drug from chemical/enzymatic degradation and enhance bioavailability [71-73].

Targeted nanozyme delivery technique is considered as boon in treatment of nuero-disorders like Parkinson's disease [74]. *In Silico*, computer aided designs are carried out prior, before the actual applica-

tion of such prodrugs to optimize the nanoparticle's surface parameters and other related aspects [75]. Recent reports made it clear that, this advancement added a plus point to discover a bolaamphiphilic prodrug, zidovudine-phosphoryl-deoxycholyl didanosine (ZPDD) containing two different drugs (zidovudine and didanosine) in a single molecule and thus simultaneously deliver two types of drugs to targeted tissues proving to be promising nanomedicine [76].

Conclusion

Prodrug approach is setting a good example for the target drug delivery process which uses simple designing process considering the site of action, targeted cell/tissue, type of administration etc. The strapping prop up for this is the large fraction of newly approved drugs that are prodrugs and similar inclination in the patent literature. Different categories of prodrugs like pro-prodrugs, mutual drugs etc have been discussed each having their own specificities to be used as a patented drug. In the current appraisal, prodrug/enzyme related therapies are conversed giving importance mainly to the targeted drug delivery process considering different carrier molecules like antibody, virus, gene, polymers etc used to direct the drug towards the site of action. Nanocarriers used for progdrug delivery stratagem procured revolution in the present era of drug administration, proving its capability as enhanced nanomedicine.

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