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Review Article

Role of Prodrugs in Solubility Enhancement of Drugs

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ABSTRACT

Solubility is one of the essential parameters to achieve bioavailability of drug in systemic circulation to produce expected therapeutic response. Nearly 40% of new drug molecules face solubility challenge. Though several techniques like micronization, crystal engineering, hydrotrophy, solid dispersion and so forth were available for solubility enhancement of poorly soluble drugs based on physical and chemical modification, prodrug approach is a vital technique amongst the other. Prodrugs are biologically inactive compound which can be metabolized in the body to produce active drug. It is estimated that currently about 10% of all world-wide approved drugs are prodrugs. This review extensively confers the role of prodrugs and the kind of promoieties used for solubility enhancement.

Keywords: Prodrugs, Solubility Enhancement of Drugs, dissolution rate, bioavailability

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. The major challenge with the design of oral dosage forms lies with their poor bioavailability. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. As for BCS class-II drugs rate limiting step is drug release from the dosage form and solubility and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class-II drugs [1]. Prodrug is biologically inactive compound which can be metabolized in the body produce drug.[2] The prodrug approach is emerged tool to overcome the various obstacles in drug formulation and targeting the chemical instability, low aqueous solubility, local irritation and toxicity.[3]

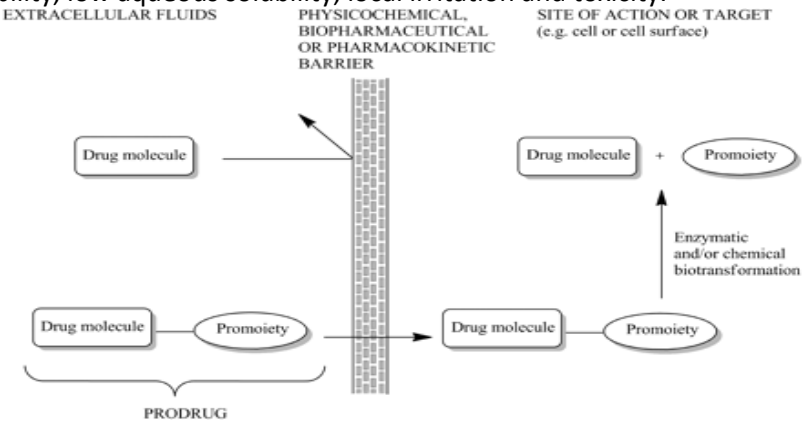

Figure No.1. A simplified illustration of the prodrug concept (Kristiina M. Huttunen et al., Pharmrev.aspetjournals.org, 2011)

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HISTORY

The term "prodrug" was introduced 55 years ago in 1958 by Albert & started to gain the popularity in 1960's. [4,5] Albert described "prodrug" or "proagent" as a pharmacologically inactive compound that is transformed by the mammalian system into an active substance by either chemical (non enzymatic) or metabolic (enzymatic) means. Later these compounds have been referred to as the "latentiated drugs" and the process as "drug latentiation" by Harper, which he described as the chemical modification of a biologically active compound to form a new compound which, upon in vivo enzymatic attack liberates the parent compound. [6] These compounds were also called as "congeners" and "bioreversible derivatives", but 'prodrug' is now the most commonly accepted term. [7-12] The first prodrugs were not necessarily meant to be prodrugs; this feature was unintentional. The antibiotic prontosil produced by Bayer was found to release the active agent sulfanilamide by reductive enzymes. Later it was marketed in 1935. [13]

In a similar way, Roche discovered the prodrug activity of the antitubercular drug isoniazid in 1952. [14] Sometimes, unintentionally developed prodrugs can reveal a less appealing truth of the drug under the development. A good example is heroin (diacetylmorphine), which was marketed during the years 1898 to 1910 as a non addictive morphine substitute to suppress cough and cure both cocaine and morphine addictions. Bayer was embarrassed to appreciate later that heroin is, infact, rapidly metabolized into morphine after oral administration. [15, 16]

The first intentionally designed prodrug is thought to be Methenamine (hexamine), produced by Schering at 1899, long before the term "pro-drug" was invented. Methenamine decomposes to formaldehyde (bactericidal) and ammonia at acidic pH and is used in treating urinary tract infection. [17]

Since the 1960s there has been an explosive increase in the use of prodrugs in drug discovery and development. The beginning of 21st century, when property based drug design became an essential part of the drug discovery and development process, has been a time of real breakthroughs in prodrugs. To emphasize the extent of the successful implementation of the prodrug approach, almost 15% of the 100 best-selling small-molecular-weight drugs in 2009 were prodrugs. One interesting example of these blockbuster prodrugs is lisdexamfetamine dimesylate (Vyvanse), the L-lysine prodrug of the psychostimulant dextroamphetamine, which was designed to have less abuse potential than other amphetamines due to the slower release of the active parent drug if inhaled or injected. [18]

It is estimated that currently about 10% of all world-wide approved drugs are prodrugs. And approximately 15% & 33% of all new drugs approved in 2001-2002 and 2008 were prodrugs respectively. Recently approved prodrugs are Ximelagatran 2004, Ciclesonide 2005, Nepafenac 2005, Lisdexamfetamine 2007, Esoterodine 2008, Fospropofol 2008, Fosaprepitant 2008, Dabigatranetexilate 2008, Tafluprost 2008, Prasugrel 2009, Dabigatranetexilate 2010, Candesartan cilexetil (Atacand HCT®) 2010, Tenofovir (viread) 2011. [19-21]

The patent literature shows a dramatic increase in numbers of prodrug patents (> 20% increase in 2010 compared to 2000), with claims for cancer treatment (37%) and antiviral agents. This increase is largely due to the rise from North American-based multinationals and some smaller drug delivery companies mirroring the overall trend. Other therapeutic classes that use a prodrug delivery method include antibiotic, anticancer and antiviral agents. List of Prodrugs

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among the world's 100 top selling drugs in 2009 are shown in the below table.

Prodrug prevalence is 15.4% among the 100 best selling small molecular weight drugs in 2008 alone. [22-26]

Table.No.1. The occurrence of prodrugs among the world's 100 top-selling pharmaceuticals in 2009.

Prodrug Name (Trade Name) and Therapeutic Area	Functional Group	Prodrug Strategy
Proton pump inhibitors		
Esomeprazole (Nexium) Lansoprazole (Prevacid) Pantoprazole (Protonix) Rabeprazole (Aciphex)	Formation of active sulfonamide form	Bioprecursor prodrugs that are converted into their respective active sulfonamide forms site-selectively in acidic conditions of stomach
Antiplatelet agent		
Clopidogrel (Plavix)	Formation of the active thiol	Bioprecursor prodrug that selectively inhibits platelet aggregation
Antiviral agent		
Valacyclovir (Valtrex)	L-Valyl ester of acyclovir	Bioconversion by valacyclovir hydrolase (valacyclovirase)
		Transported predominantly by hPEPT1
		Oral bioavailability improved from 12–20% (acyclovir) to 54% (valacyclovir)
Hypercholesterolemia		
Fenofibrate (Tricor)	Isopropyl ester of fenofibric acid	Lipophilic ester of fenofibric acid
Antiviral agent		
Tenofovir disoproxil (Atripla)	Bis-(isopropyloxy-carbonyloxymethyl) ester of tenofovir	Bioconversion by esterases and phosphodiesterases
		The oral bioavailability of tenofovir from tenofovir disoproxil is 39% after food
Psychostimulant		
Lisdexamfetamine (Vyvanse)	L-Lysyl amide of dextroamphetamine	Bioconversion by intestinal or hepatic hydrolases
		Reduced potential for abuse due to prolonged release of active drug
Influenza		
Oseltamivir (Tamiflu)	Ethyl ester of oseltamivir carboxylate	Improved bioavailability compared with oseltamivir carboxylate, allowing oral administration

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Prodrug Name (Trade Name) and Therapeutic Area	Functional Group	Prodrug Strategy
Hypertension		
Olmesartan medoxomil (Benicar)	Cyclic carbonate ester of olmesartan	Improved bioavailability compared with olmesartan, allowing oral administration
Immunosuppressant		
Mycophenolate mofetil (CellCept)	Morpholinyl ethyl ester of mycophenolic acid	Improved oral bioavailability with less variability
Glaucoma		
Latanoprost (Xalatan)	Isopropyl ester of latanoprost acid	Bioconversion by esterases

CLASSIFICATION

Depending upon the constitution, lipophilicity, method of bioactivation and the catalyst involved in bioactivation, prodrugs are classified into two categories; Carrier linked prodrug and Bioprecursor prodrug.[27]

A. Carrier linked prodrugs

Carrier linked prodrug consists of the active drug covalently linked to an inert carrier or transport moiety, generally ester or amide. Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically. The Prodrug and carrier released after in vivo enzymatical or non-enzymatical attack must be nontoxic. [28]

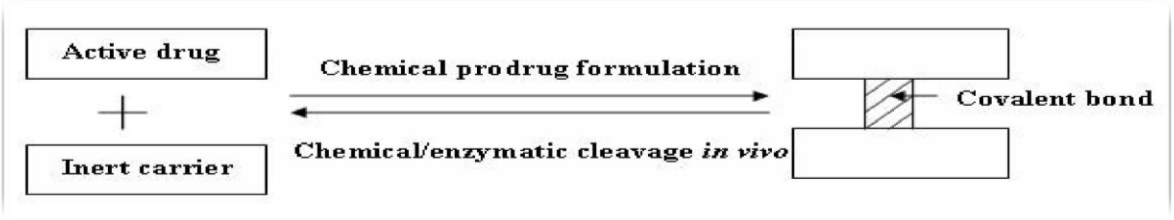

Figure No.2. Carrier linked prodrug (V.S. Tegeli et al., IJDFR, 2010)

B. Bioprecursors

They are inert molecules obtained by chemical modification of the active drug but do not contain a carrier. Such a moiety has almost the same lipophilicity as the parent drug and is bioactivated generally by redox biotransformation only enzymatically. e.g. Aryl acetic acid NSAID such as Fenbufen from aroyl propionic acid precursors.

Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties. The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety. Hence, the carrier linked prodrugs have a major drawback that they are linked through covalent linkage with specialized nontoxic protective groups or carriers or promoieties in a transient manner to alter or eliminate undesirable properties in the parent molecule.

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Depending upon the nature of carrier, the carrier linked prodrug may further be classified into, [29]

Double prodrug

Double prodrug also termed as 'Pro-prodrug' , is a prodrug further derivatized in a fashion such that only enzymatic conversion to prodrug is possible before the later can cleave to release the active drug. e.g. Cefpodoxime proxetil

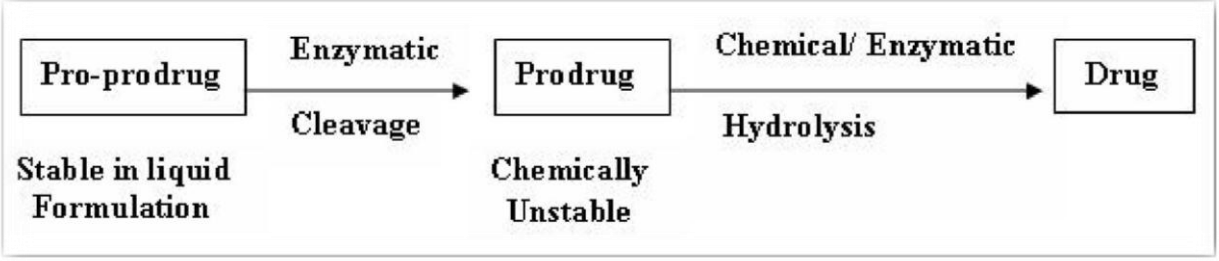

Figure No.3. Double prodrug (V.S. Tegeli et al., IJDFR, 2010)

Macromolecular prodrug

Macromolecules like polysaccharides dextrans, cyclodextrins, proteins, peptides and polymers may be used as carriers to form the macromolecular prodrugs. e.g. Naproxen-2-glyceride.

Site specific prodrug

In this approach, prodrug is designed using a carrier which acts as a transporter of the active drug to a specified targeted site. e.g. Progabide-Diethyl stilbesterol. [30]

Mutual Prodrug

A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. [31] e.g. Estramustine is a mutual prodrug composed of a phosphorylated steroid (17- α- estradiol) linked to Nor-mustard, an anti-androgenic drug through a carbamate linkage. The steroid portion of the molecule helps to concentrate the drug in prostrate. The carrier selected may have the same biological action as that of the parent drug to give synergistic action or some additional biological action that is lacking in the parent drug, thus ensuring some additional benefits. The carrier can also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effect of the parent drugs as well. [32, 33]

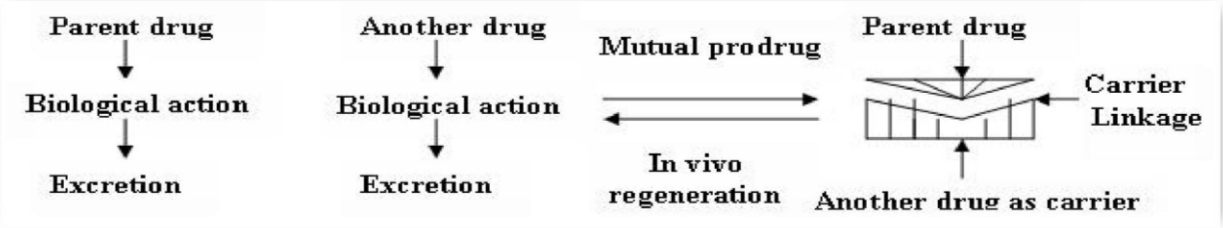

Figure No.4. Mutual prodrug (V.S. Tegeli et al., IJDFR, 2010)

SOLUBILITY ENHANCEMENT OF DRUGS USING PRODRUGS

Poor aqueous solubility is considered as a serious problem limiting the therapeutic use of numerous drugs and drug candidates. Among

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various strategies used to overcome this drawback, prodrug approach is one of the efficient method. Prodrugs designed to overcome low aqueous solubility are used not only to enhance the oral bioavailability, but also for the preparation of parenteral or injectable drug delivery.[34-36] Prodrugs can increase the aqueous solubility of the parent drug molecule,

- By decreasing hydrogen bonding and consequent crystal lattice packing, which lead to lower melting point of the parent drug molecule.
- By increasing the polarity of the drug molecule. Promoieties can be connected to drug molecules in various different ways depending upon the functional groups present in the drug molecule and the desired way to release the parent compound. Different types of promoieties like ionizable or ionic promoieties and neutral promoieties can be used depending upon the desired properties of the drug.

Phosphate ester prodrugs

Phosphate mono esters contain two ionizable groups and they exist predominantly as dianions at physiological pH 7.4, providing high aqueous solubility. One frequently employed means of improving the aqueous solubility of a drug is by the use of esters and amides of phosphoric acid.

- They offer high chemical stability, often even higher than the parent drug & are especially useful for drugs that require a high dose & exhibit dissolution-rate limited absorption.[37]
- Phosphate prodrugs rapidly release their active parent drug molecule by endogenous phosphatases, like alkaline phosphatase, which is particularly abundant on the brush border (or apical surface) of the enterocytes and in plasma. [38, 39]

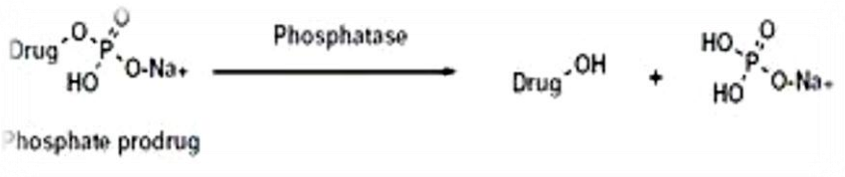

Figure No.5. Bioconversion of phosphate prodrug into drug by phosphatases

- After oral administration, the phosphate group is cleaved before absorption, and therefore, the ionizable prodrug structure does not decrease the permeability of the parent drug molecule.
- Thus, they show rapid enzymatic bioconversion. However some phosphomonoester prodrugs of sterically hindered secondary and tertiary alcohols suffer a slow rate of enzymatic conversion.[40] This problem can be overcome by using a suitable linker to attach the phosphate promoiety to the parent.
- Phosphate promoieties are often attached to the parent drug via an oxymethyl spacer group.

Phosphate esters are very effective and widely used prodrug structures for improving the aqueous solubility for both oral and parenteral drug delivery. [41, 42]

The major applications of water soluble phosphate prodrugs are described below with examples that have been approved for marketing or that are currently or have been in clinical trials. Some of the phosphate prodrugs marketed are Dexamethasone phosphate, Stachyflin phosphate & oxyphenbutazone phosphate, Clindamycin phosphate, Etoposide disodium phosphate, 20-Phosphoryloxymethyl camptothecin, Aminodarone disodium phosphate, loxapine phosphate, bisantrene phosphate, diethylstilbesterol disodium phosphate, Entacapone phosphate.

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Examples (Joanna B. Zawilska et al., Pharmacological Reports, 2013)

Prodrugs used for parenteral administration

Fosphenytoin sodium salt

Fosphenytoin sodium salt (Cerebyx®), is an example of a phosphonooxymethyl spacer prodrug linked to the amine group of phenytoin. 7500-fold increased aqueous solubility of prodrug (140 mg/ml) when compared to drug (0.019 mg/ml). It is used as an anti-epileptic agent.

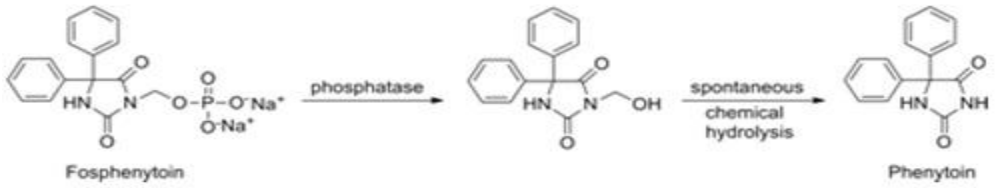

Figure No.6. Bioconversion of Fosphenytoin sodium salt into phenytoin

Fosfluconazole (Procif®)

Phosphate ester of Fluconazole, an antifungal intended for parenteral use. Increased aqueous solubility of fosfluconazole (over 300 mg per ml) compared to drug.

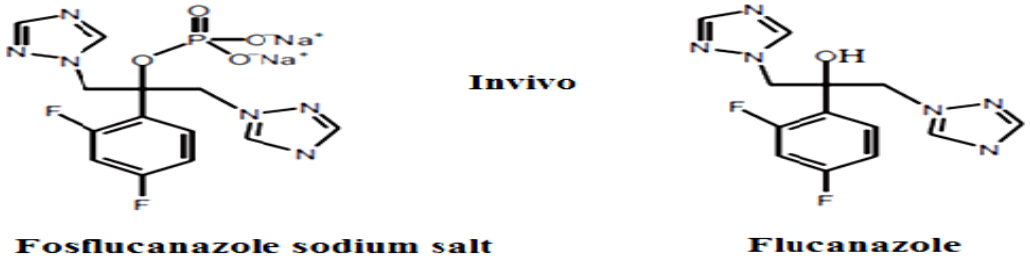

Figure No.7. Bioconversion of Fosfluconazole sodium salt into Fluconazole

Phosphono oxy methyl propofol

Phosphono oxymethyl ether of Propofol, intended for parenteral administration. 3300-fold increased aqueous solubility of prodrug (500µg/ml) when compared to drug. It is used for anesthetic purpose.

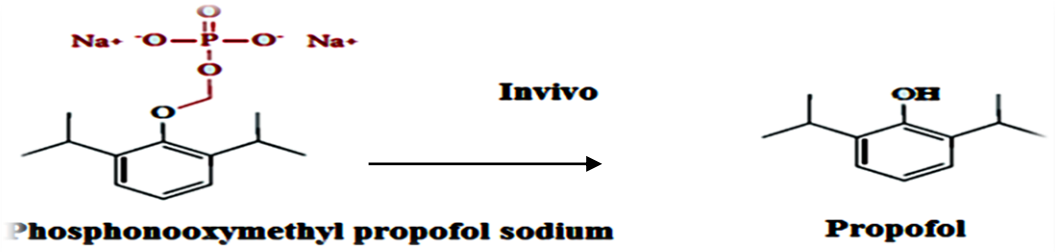

Figure No.8. Bioconversion of phosphonooxymethyl propofol sodium into propofol

Propofol phosphate

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Phosphate ester of propofol intended for parenteral administration. Significantly increase the aqueous solubility of propofol (150µg/ml)**.** Bioconversion to propofol after intravenous administration is significantly slower when compared with phosphonooxy methyl propofol. It is used as an anesthetic.

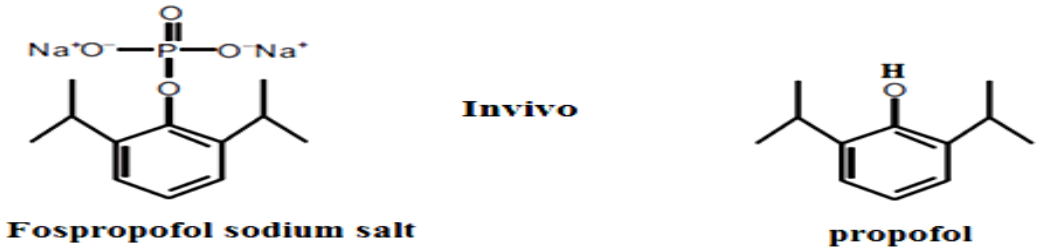

Figure No.9. Bioconversion of propofol sodium phosphate into propofol

Estramustine phosphate (Emcyt®)

Phosphate ester of Estramustine, an anti-mitotic, marketed both as injectable and oral formulations for the treatment of prostate carcinoma since the mid 1970s. The aqueous solubility of prodrug increased 40-folds when compared to drug.

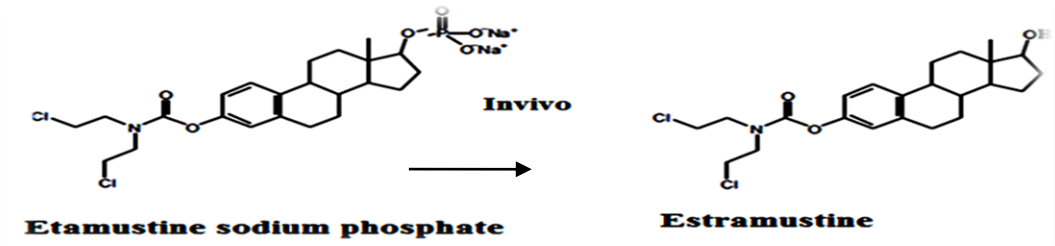

Figure No.10. Bioconversion of Estramustine sodium phosphate into Estramustine

Fludarabine phosphate

Until recently, Fludarabine phosphate was marketed only for parenteral use. 9-fold increased aqueous solubility of prodrug when compared to drug.

Figure No.11. Bioconversion of Fludarabine phosphate into Fludarabine

All of these phosphate prodrugs have significantly improved aqueous solubilities and consequently enhanced absorption, bioavailability, patient acceptance/ compliance compared to their parent drug.

Prodrugs used for oral administration

Miproxifene phosphate

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Phosphate ester of Miproxifene, used as an anti cancer agent. Aqueous solubility of prodrug (>140 mg/ml) at pH 7.4 increased by 1000-folds when compared to drug (0.019 mg/ml) bioavailability enhanced to 28.8% in rats and 23.8% in the dog.

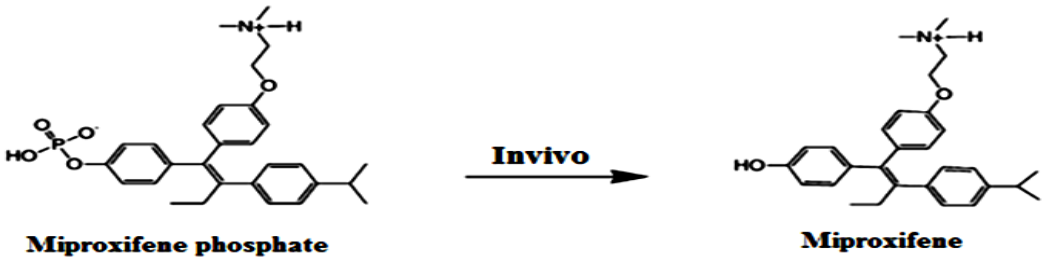

Figure No.12. Bioconversion of Miproxifene phosphate into Miproxifene

Fosamprenavir (Telzir®)

Phosphate ester of Amprenavir is a HIV protease inhibitor. More simplified and patient compliant dosage regimen, aqueous solubility of Fosamprenavir prodrug (41µg/ml) is increased by 10 folds when compared to drug (0.3 mg/ml).

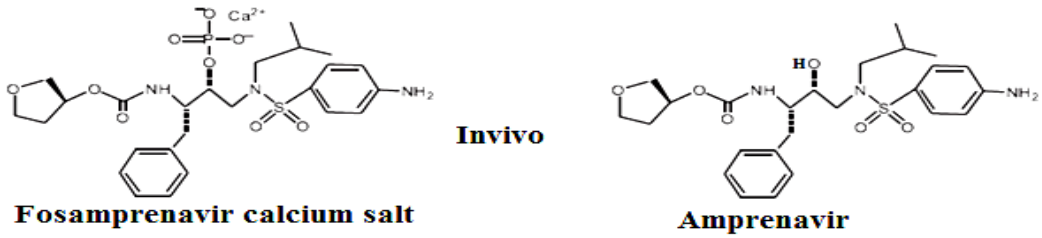

Figure No.13. Bioconversion of Fosamprenavir calcium salt into Amprenavir

Fosgliclazide

Phosphate monoester of Gliclazide is an antidiabetic drug. Aqueous solubility of Fosgliclazide prodrug is increased by 920-fold when compared to drug. It is an example of a phosphonooxymethyl spacer prodrug linked to the amine group of Gliclazide.

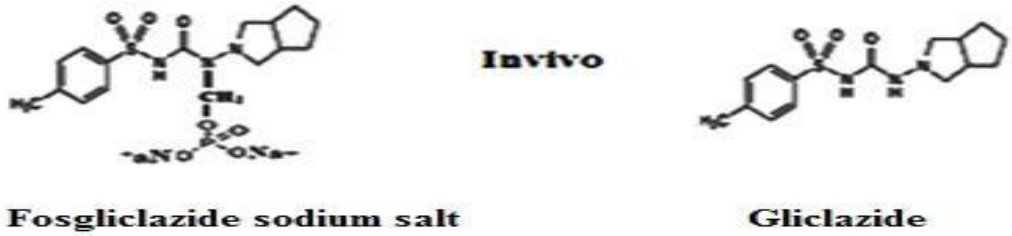

Figure No.14. Bioconversion of Fosgliclazide sodium salt into Gliclazide

Amino Acid Ester prodrugs

Amino acids are other widely used ionizable group introduced to the parent drug molecule to compensate for poor aqueous solubility.

- Amino acid esters or amides and amino alkyl esters or amides are rapidly bioconverted to their active species by a variety of esterases, amidases, and/or peptidases either in plasma or other tissues, and can be used for both oral and parenteral drug delivery.[43]

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- These get ionizable, either anionic or cationic. Promoieties can be attached to a hydroxyl, amine, or carboxylic acid group of the parent drug molecule. [41, 42]

Examples (Anitha Sriram. et al., IJMCA, 2014)

L-Lys-dapsone HCl

It is a lysine amide prodrug of dapsone (antileprosy drug) It is developed prodrug for improved oral and parenteral drug delivery of a poorly water-soluble amine. 400-fold increased aqueous solubility of prodrug (> 65) when compared to drug (0.016). [44]

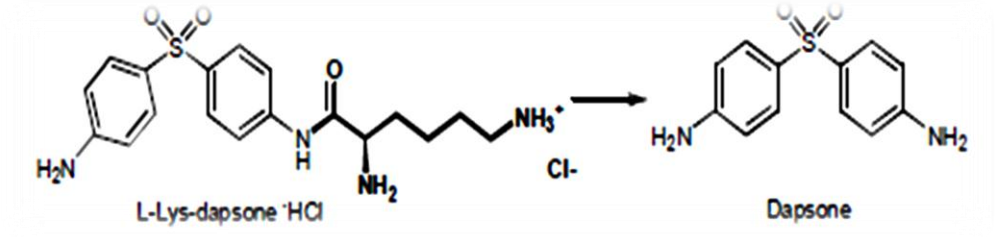

Figure No.15. Bioconversion of L-Lys-dapsone.HCl prodrug to Dapsone

Valacyclovir (Valtrex ®)

It is an L-valyl ester of acyclovir, a purine nucleoside used for the treatment of viral infections, like herpex simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV, HSV-3), Epstein-Barr virus, and cytomegalovirus. After oral administration, the bioavailability of valacyclovir is over 50% when compared to that of acyclovir, which is only between 15% and 30%.

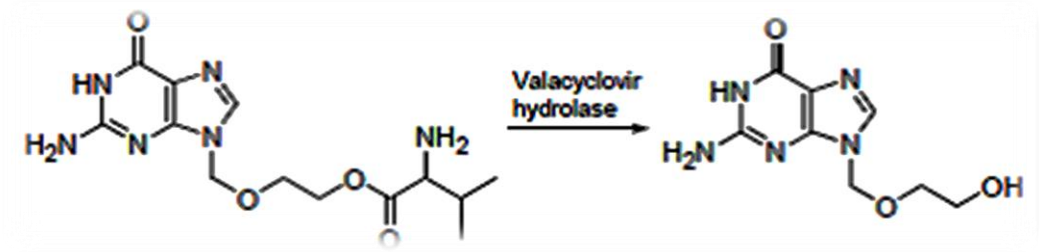

Figure No.16. Bioconversion of valacyclovir to acyclovir by valacyclovir

Alprazolam HCl

It is an amide prodrug of Alprazolam. 7267-fold increased aqueous solubility of prodrug (109 mg/ml) when compared to drug (0.015mg/ml).

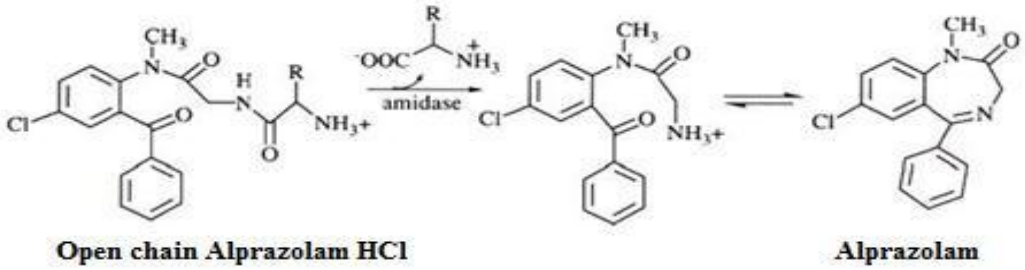

Figure No.17. Bioconversion of Alprazolam HCL to Alprazolam

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CAM 4562

It is a dimethyl glycine ester prodrug of CAM 4451, a nonpeptide tachykinin NK1 receptor antagonist that has been found to be involved in the regulation of pain and some autonomic reflexes and behavior, Aqueous solubility of prodrug (3 mg/ml) at pH 7.4 increased by 1000-folds when compared to drug (< 0.002 mg/ml).

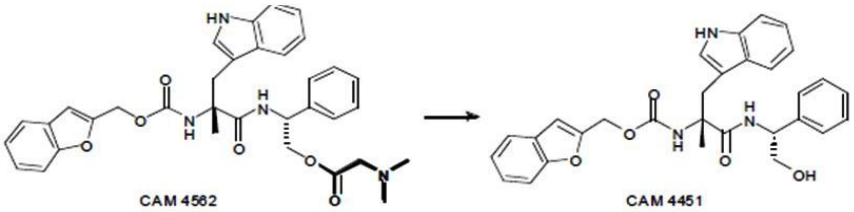

Figure No.18. Bioconversion of CAM 4562 to CAM 4451

CAM 4562 and L-Lys-dapsone are investigational ester and amide prodrugs for improved oral and parenteral drug delivery of a poorly water-soluble alcohol and amine, respectively.

However, in many cases amino acid ester and amide prodrugs suffer from poor aqueous stability and/or incomplete *in-vivo* bioconversion, and therefore, phosphate prodrugs are preferred prodrug structures to improve the aqueous solubility of parent drugs. Paradoxically, amino acid esters and amides can not only be used for improvement of poor aqueous solubility but also for enhancement of permeability to improve oral drug delivery and systemic exposure of parent drugs.

Sugar moiety prodrugs

Recently, sugar moieties, such as glucose, galactose, or glucuronic acid, have been utilized to improve the aqueous solubility of poorly water-soluble drugs.

- The sugar moiety can be attached to the hydroxyl or amine group of the parent drug molecule via various self-immolative spacers, and these prodrugs are bioconverted to their parent drug molecules by β-glucosidase, β-galactosidase, or β-glucuronidase.
- However, the sugar-spacer moiety can also be hydrolyzed from the ester, carbamate, or carbonate bond between the parent drug and the spacer by esterases.

Example

Sugar-based anticancer prodrugs, like the glucuronide prodrug of Etoposide which contains a hydroxyl moiety that serves as a synthetic handle, have proved to be not only more water-soluble but also tumor-selective prodrugs. 200-fold increased aqueous solubility of prodrug (20 mg/ml) when compared to drug (0.1 mg/ml).[42]

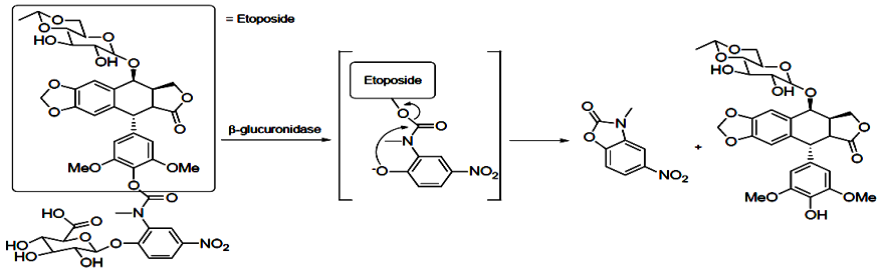

Figure No.19. Bioconversion mechanism of Glucoside-based spacer prodrug of Etoposide (Schmidt F et al., Bio. org. Med. Chem, 2003)

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Sulfate Ester prodrugs

Sulfate esters are known to be chemically stable and they readily increase the aqueous solubility of the parent compound. However, some past reports of sulphate esters indicate that they are not effectively enzymatically cleaved in-vitro or in-vivo tests.[45, 46] This enzymatic stability of sulphate esters reduces their usefulness as potential water-soluble prodrugs. However, a sulphate group could also be introduced with enzymatically labile linker so that enzymatic hydrolysis would be carried out by various esterases instead of sulfatases.[47]

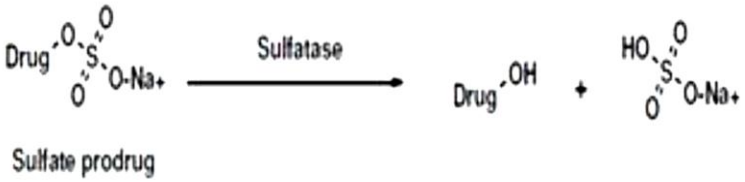
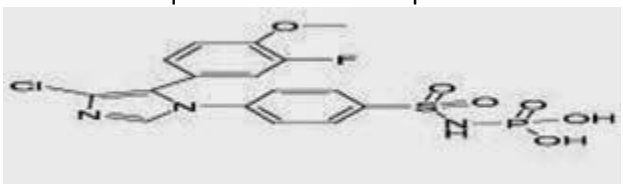


Figure No.20. Bioconversion of sulfate prodrug into drug by sulfatases

Some may exhibit poor aqueous solubility at physiological pH 7.4. The sulfonamide group is weakly acidic and the pKa of the group is usually too high to affect solubility at pH 7.4.

Examples

Sulfony phosphoramidic acid derivatives of the selective COX-2 inhibitor, Cimicoxib show good solubility at neutral pH, enabling formulation as aqueous solutions for parenteral administration.[48]



FigureNo.21.Chemical structure of Sulfony phosphoramidic acid derivative of Cimicoxib (Almansa C et al., J. Med. Chem; 2004)

Dicarboxylic Acid Hemiester prodrugs

These are generally used to increase the water solubility of highly lipophilic compounds. Hemi succinate esters & hemi glutarate esters come under this category.

Hemi succinate esters

A hemi succinate group can be conveniently used to increase water solubility, as it contains a free carboxylic group, which is suitable for the formation of dissociated salts. They have been commonly used in the past, solution instability together with slow and incomplete bioconversion invivo limit their utility.

Examples

- Chloramphenicol, Prednisolone, Methylprednisolone hemisuccinates, Prednisolone sodium succinate, Hydroxydione sodium succinate, Oxazepam sodium succinate, & Cinazepam.
- Cinazepam, a novel benzodiazepine anxiolytic drug suitable for intravenous injections. Some improvement of solution stability & enzymatic liability may be gained by using longer hemiester such as glutarate.

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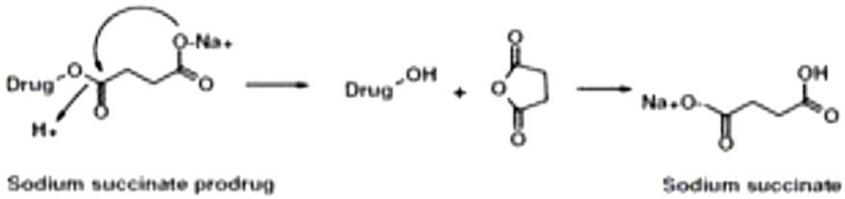

Figure No.22. Bioconversion of succinate prodrug into drug

Polyethylene Glycol Esters (PEGs)

Promoieties with no ionizable or charge containing groups can also be used to increase aqueous solubility. One strategy for high-melting compounds is to decrease the melting point by masking groups that are able to form intermolecular hydrogen bonds. Examples of this approach are the poly ethylene glycol prodrugs.

- Polyethylene glycols (PEGs) are linear or branched neutral oligomers or polymers of ethylene oxide with a broad molecular weight range (300-10,000,000 g/mol).
- These amphiphilic polymers have also been used to improve the aqueous solubility of poorly water-soluble drugs for both oral and parenteral drug delivery.
- PEG promoieties can be attached to the hydroxyl or amine group of the drug via various self-immolative spacers and linked to the spacer via an ester, amide, carbonate, or carbamate bond that undergoes either chemical or enzymatic cleavage in the bioconversion process.

Examples

- This prodrug approach has been applied to chemotherapeutic agents, Paclitaxel (Taxol®), Camptothecin,[49] and Daunorubicin.
- The prodrug of Mebendazole have lower meting points and up to 16-times higher aqueous solubility, while still maintaining the optimal lipophilicity for absorption.[50]

Sulfoxide Prodrugs

Sulfoxides and sulfones are of immense interest because of their extensive applications in organic chemistry. The oxidation of sulfides to sulfoxides or sulfones has been the subject of extensive studies.[30] There are many reagents available for oxidation of sulfides such as halogens, nitrates, oxygen, urea-hydrogen peroxide adduct and hydrogen peroxide. Although it is powerful oxidant, the reactions of hydrogen peroxide are generally slow and challenge is to overcome the kinetic barrier in cost effective and 'green chemical' ways.

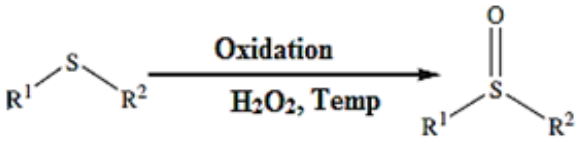

Figure No.23. General scheme of Sulfoxidation

Example

Sulindac sulfoxide:

It is a water-soluble prodrug of the sulindac, NSAID. This is a bioprecursor prodrug that does not contain a promoiety, but instead, its inactive sulfoxide form is reduced to the active sulfide form after oral

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absorption. 100-fold increased aqueous solubility of Sulindac sulfoxide (3.3 mg/ml) when compared to pharmacologically active sulphide drug (0.03µg/ml).[42]

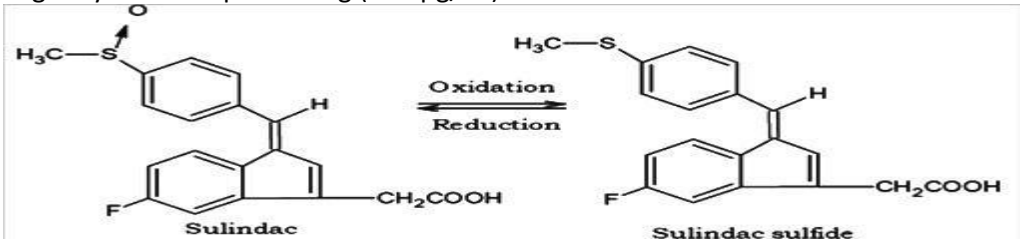

Figure No.24. Bioconversion of the Sulindac Prodrug to Sulindac sulfide
(Schmidt F et al., Bio. org. Med. Chem, 2003)

CONCLUSION

The prodrug strategy is one of the most promising approaches to enhance the solubility and in turn bioavailability of drug. Introduction of new chemical entity in the market is very expensive and time consuming process. Thus R&D oriented pharma companies are trying to alleviate solubility problems of existing drugs. Prodrugs remain an effective tool to overcome those barriers. Hence legitimate choice of promoieties surmounts pharmacokinetic barrier in formulating a chemical entity. In prospective view emergence of prodrug is a boon for pharma industry and to mankind.

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