PRO-DRUG DEVELOPMENT

ANJALI PALWAR, MOHD.ARSHAD, ANJALI,*
AMAN BHARTI, ANKIT SINGH, SUNIL PRATAP SINGH
RAJA BALWANT SINGH ENGINEERING TECHNICAL CAMPUS, BICHPURI (AGRA) - 283105

Introduction

- Prodrug is one of the effective methods of modern research in the field of medicine.[4]
- The development of prodrug have gained increasing more importance in current medication system and therapy.[4]
- Prodrugs refer to a pharmacologically inactive compound which is transformed into an active substance by either chemically or metabolic process.[4]
- Prodrug in modern therapy is actually demonstrated by the fact that in the last ten years several books in this field have been published and thousands of article in scientific database are investing new potential molecules.[4]
- About half or most of prodrugs are hydrolyzed to the active form in particular by hydrolysis of ester.[4]
- Now a day's approximately 10% of drugs used in therapy are administered as prodrug.[4]

The concept of prodrugs was first described in the late 1950s, but prodrugs have existed for more than a century.[1]

Aspirin is one of the first prodrug that was widely used and also first marketed prodrug in 1899.[1]

It turns into a substance called salicylic acid after it enters the body.[1]

In the past, the prodrugs used to be considered as last resort in drugs development not only is this no longer the case. But now days the prodrug approach is considered at very initial stages of drugs research and development.[2]

Making a prodrug indeed means dealing with a new chemical entity, which eventually may save time money and efforts.[2]

History of prodrugs

1. Chloramphenicol is the first synthesized drugs as prodrugs. The concept of prodrug, the concept of prodrug was intentionally used for the first time by the Parke Davis Company.
2. The Parke Davis Company modifies the structure of chloramphenicol in order to improve the antibiotics bitter taste and poor solubility in water.
3. Chloramphenicol sodium succinate with a good water solubility and chloramphenicol palmitate used in the form of suspension in children. Were two synthesized prodrugs form of chloramphenicol?
4. Another historical prodrugs was synthesized German scientific. Aspirin is that historical prodrugs.
5. Dresser introduced aspirin into medicine in 1899.
6. Acetanilide was the first compound that fulfilling the classicalteria of prodrugs. Introduced into the medical practice by Cahn and help in 1867 as antipyretic agents.

7. Acetanilide is hydrolated to biologically active acetaminophen.

What are prodrugs?

The international union of pure and applied chemistry. Defines a prodrug as a chemical that is transformed before it has pharmacological effects. [1]

A prodrug can be defined as a prodrug substance that is inactive in the intended pharmacological action and it must to be converted in to the pharmacologically active agent by metabolic physio-chemically transformation.[1]

In other words, after you take prodrug, it changes in your body before it starts working.

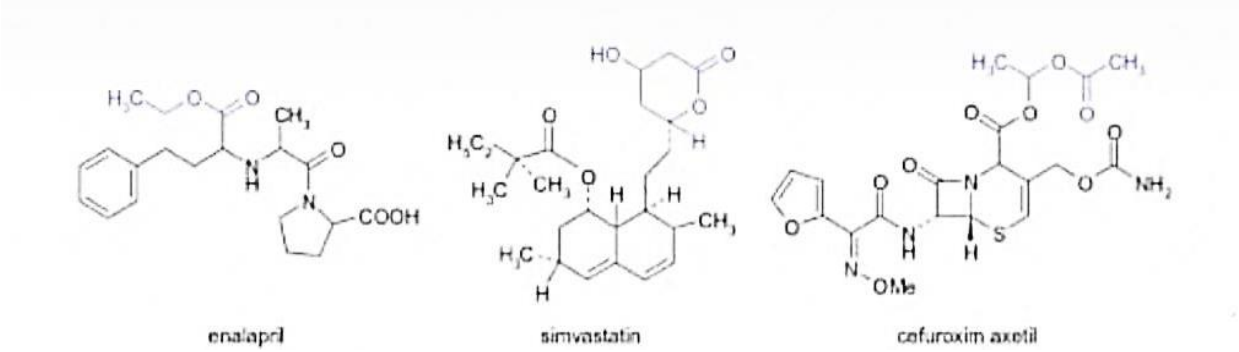


Fig.1 the chemical structure of a few frequently used prodrugs.[4]

The prodrug concept has been used to improve undesirable properties of drug.

The actual term 'prodrug' was introduced for the first time by "ADRIAN ALBERT" for drug's that are inactive by themselves but which formed an active derivative by biotransformation.

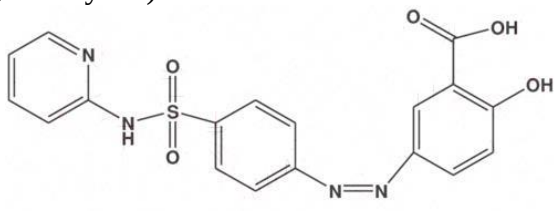
The concept was completed by "HARPER" in 1959 was introduced the term of drug latentiation referring to drug that were specifically designed to require bio-activation.

A prodrug is a chemically modified inert precursor of the drug that on the biotransformation liberates the pharmacologically active parent compound. A prodrug is also called proagent, bio reversible derivative of latentiated drug. The design of prodrug approach is also called drug latentiation.

The place and speed of biotransformation are closely related to chemically structure, as well as the pharmacokinetic properties of the molecules.

The concept of prodrug has to be differentiated from drugs that are active of their own, but by biotransformation are forming one or more active metabolites and the biologically effects occur as a common result of the original drug and metabolites.

In some cases, a prodrug may consist of two pharmacologically active drugs that are coupled together in a single molecule, so that each acts as a promoiety for the others. Such derivative are called "CODRUGS".[4] (E.g. sultamicillin, sulfasalazine, benorylate)



Sulfasalazine

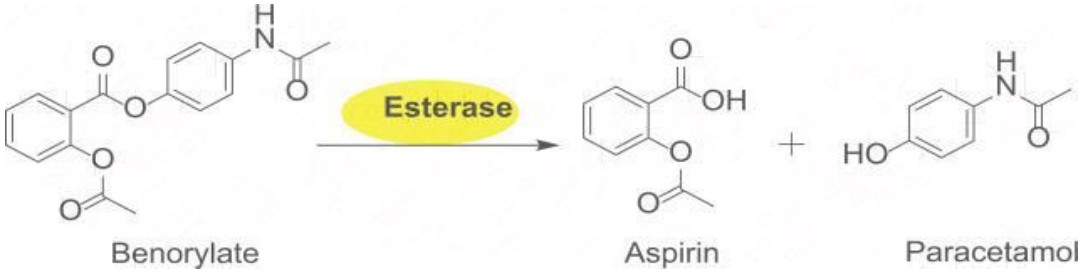


Fig.2 structures of some prodrugs

Ideal properties of prodrugs

The ideal properties of a prodrug are as follows:

- Drugs and the carrier linkage must be cleared in vivo.
- It should not have intrinsic pharmacologic activity.
- IT should rapidly transform, chemically or enzymatically, into that active form where desired.
- The metabolic fragments, apart from the active drug, should be nontoxic.

The purpose of designing prodrugs

The purpose of designing prodrugs are mainly based on two objectives:-

1. Improving bioavailability when the drug candidate is not drug like due to unfavorable physical properties as:-
   - Poor water solubility
   - Low lipophilicity
   - Chemical instability
   - Unacceptable taste or smell
   - Local irritation, pain

2. Improving bioavailability when the drug candidate is not drug-like, due to pharmacokinetics properties

   - Low bioavailability
   - Poor penetration through biological membranes
   - Increased first-pass metabolism
   - Slow absorption by parental route
   - Rapid absorption/elimination instead of long lasting effect
   - Lack of specificity in certain tissues

   The main specific objective of prodrug design is to optimize unfavorable physiochemical properties to increase chemical and metabolic stability to achieve planned delivery.[4]

3. Pharmaceutical objectives
   - To improve solubility, chemical stability, and organoleptic properties.
   - To reduce problem related with the pharmaceutical technology of the active agent.
   - To decrease irritation and pain after local administration.

4. Pharmacokinetic objective
   - To improve absorption (oral and non-oral routes).
   - To increase organ/tissue selective delivery of the active agent.
   - To decrease presystemic metabolism to improve time profile.

5. Pharmacodynamics objectives
   - To decrease toxicity and improve therapeutic index

- To design single chemical entities combining two drugs (co-drugs strategy).

The prodrug is used to overcome many complication related to biopharmaceutical, pharmacokinetic or pharmacodynamics obstacles, including poor chemical stability, solubility limitation lack of site specificity, extensive drug metabolism passing through biological barriers, exploiting endogenous metabolic pathways, toxicity.

Prodrugs design to give optimal oral bioavailability and consequent therapeutic effects, the prodrug is used for the optimization of newly discovered chemical entities.

These approaches improve the properties of already marketed drugs.[3]

Classification of prodrugs

Prodrugs can exist naturally such as many phytochemical/botanical constituents and endogenous substance. They can result from synthetic or semisynthetic process.[2]

There are potentially many methods of classifying prodrugs.

These could include:

1. Based on therapeutic categories for example, anticancer prodrugs. Antiviral prodrugs.

2. Based on the categories of chemical linkage or moiety/carriers that attach to the active drug; for example esoteric prodrugs, glycoside prodrugs, bipartite prodrugs.

3. Based on functional categories using strategic approaches to circumvent deficiencies inherent to the active drugs; for example,

- Prodrugs for improving site specificity
- Prodrugs to bypass high first pass metabolism.

1. Classification based on conversion in body:

(i) Type Ist Prodrugs turn into their active forms inside the cells. These are also called intracellular prodrugs.

(ii) Type IInd Prodrugs turns into their active forms outside of cells such as in blood or other fluids. These are also called extracellular prodrugs.[3]

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

2. Classification based on chemical criteria

(i) Carrier linked prodrugs or simple prodrugs-

They are generally esters or amide carrier linked prodrugs are those ones where the active drug is covalently linked to an inert carrier or transport moiety. Such prodrugs modify the lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage, either chemically or enzymatically.[6]

These are also called conventional prodrugs obtained by chemical derivatization the desired objective is to optimize transport properties; as on the parent molecule are grafted functional groups that promote absorption.[4]

Ideal properties of carrier

- It does not alter the structure of prodrug until reaches the site of action.
- It must be nontoxic and unstable molecule.
- It does not affect the chemical or enzymatic action of drug and helps to release in active form of drugs.
- It must bear biochemical inertness
- The drug at the location of action does not alter by the carrier and maintained by carrier.

Example- chloramphenicol succinate

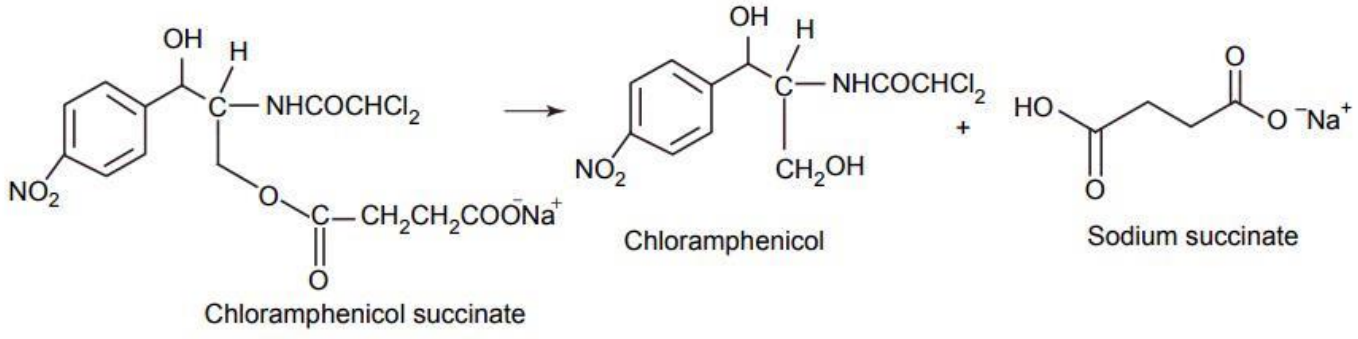


Fig.4 Chloramphenicol[6]

It consist the attachment of a carrier group to the active drug to alter its physiochemical properties.

The succeeding enzymatic or non-enzymatic mechanism releases the active drug moiety

Carrier linked prodrugs can be divided into 3 categories:

- ➔ **Bipartite prodrug**
- ➔ **Tripartite prodrug**
- ➔ **Mutual prodrug**

(I) Bipartite Prodrug

- Bipartite prodrug consist one carrier (group) directly attached to the drugs.
- The attached carrier have greatly modified lipophilicity in such prodrugs the active drug is released by hydrolytic cleavage either chemically or enzymatically.[5]
- E.g. Tolmetin- glycine prodrug

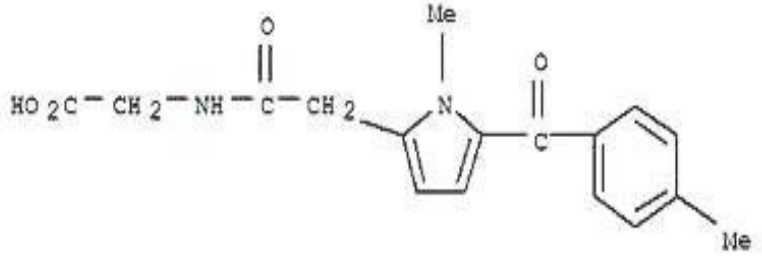
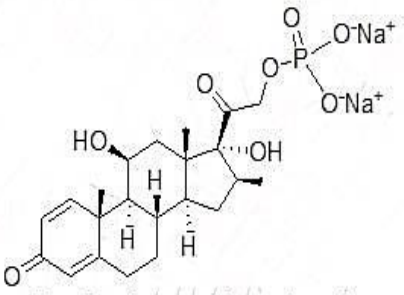
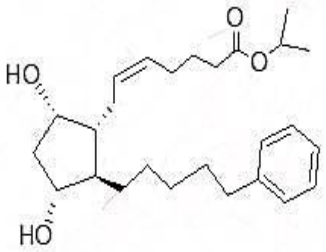


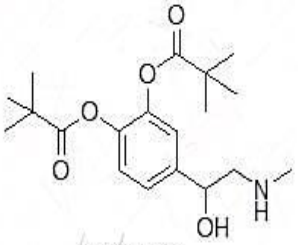
Fig.5 Tolmetin



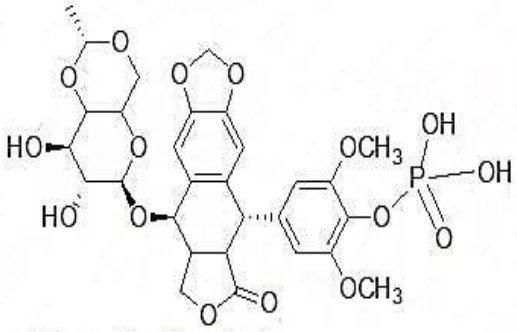
Prednisolone sodium phosphate



Latanoprost isopropyl ester



Dipivefrin

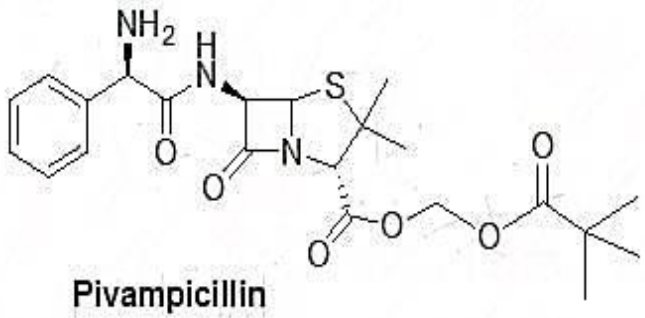


Etoposide phosphate

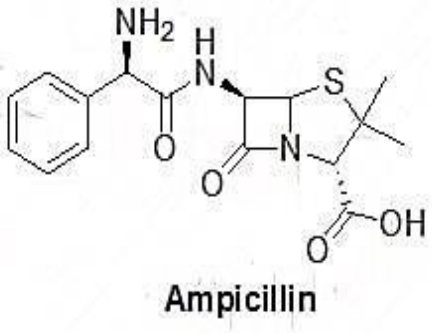
Most of the carrier linked prodrug is bipartite.

(ii) Tripartite Prodrug: in this type of prodrug uses a spacer or linkage between the drug and a pro moiety.

- To overcome the unstable nature of bipartite prodrug due to the inherent nature of the drug promoiety bonding. Tripartite prodrugs are developed and synthesize.
  EX: - pivampicillin and bacampicillin are some example of tripartite prodrug.



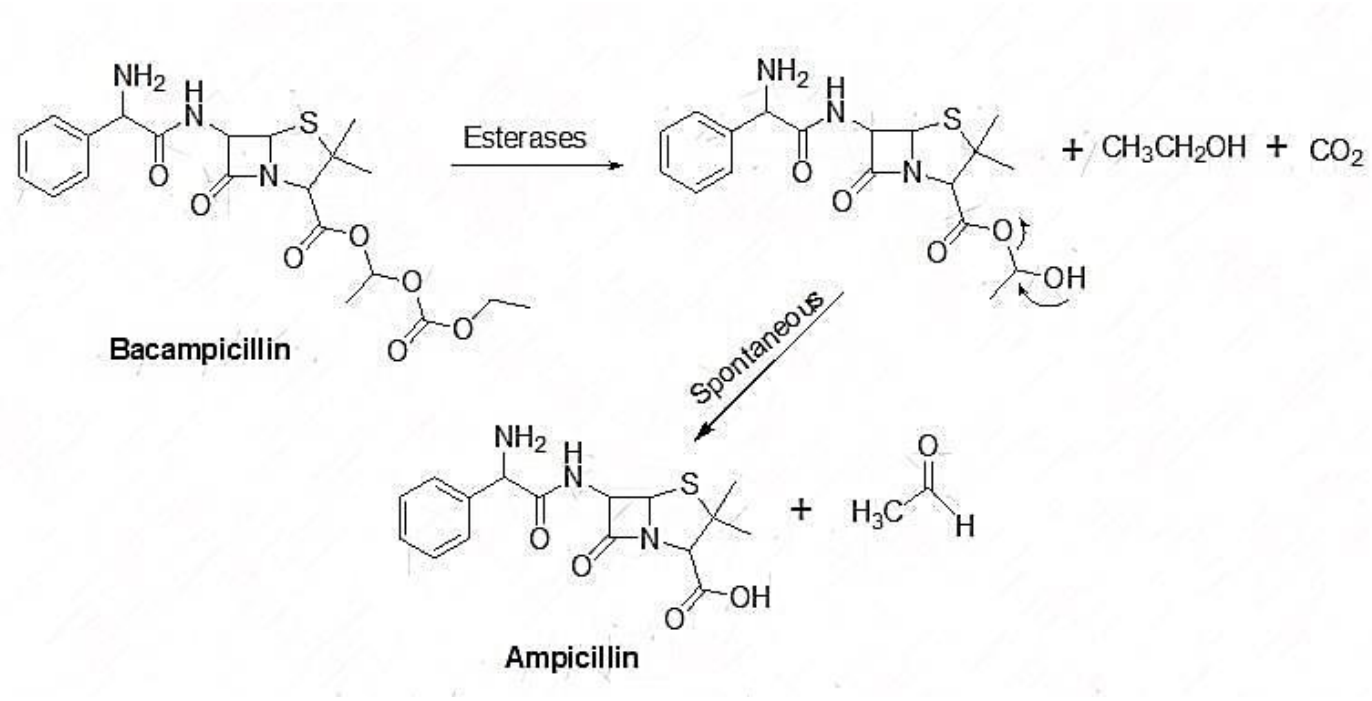
Pivampicillin



Ampicillin

Fig.6

- It consists of pivaloyloxymethly ester, B lactam, ampicillin, and $–CH_2-$ group as a linker to connect to ampicillin and the pivallic acid.
- Pivampicillin has better bioavailability than ampicillin because the ester group creates higher lipophilicity.[5]



(iii) Mutual prodrugs: these are the prodrugs which consist of two pharmacological active agent coupled together so that each acts as a promoiety for the other agent and vice versa.

- In this type of prodrug the carrier is a synergistic drug with the drug to which it is linked. It is both a bipartite or tripartite prodrugs.
- A mutual prodrug has two potent agent bound together in such a way acts as two synergistic drugs linked to each other where one drug serves as the carrier for the other and opposite.

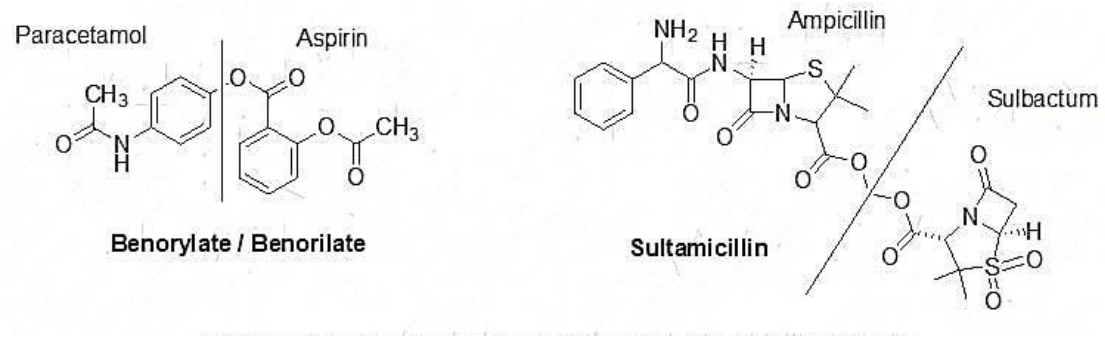


Fig.7

EX; benorylate and sultamicillin are the some ideal examples of mutual prodrugs.

In benorylate aspirin is linked covalently to pracetamol through an ester linkage.

This drug is suitable for improved analgesic power and decrease gastric irritation.[5]

Bio precursors

Bio precursor does not contain a carrier. They are the prodrugs which are inert molecule and obtained from the chemical modification of the active drug.

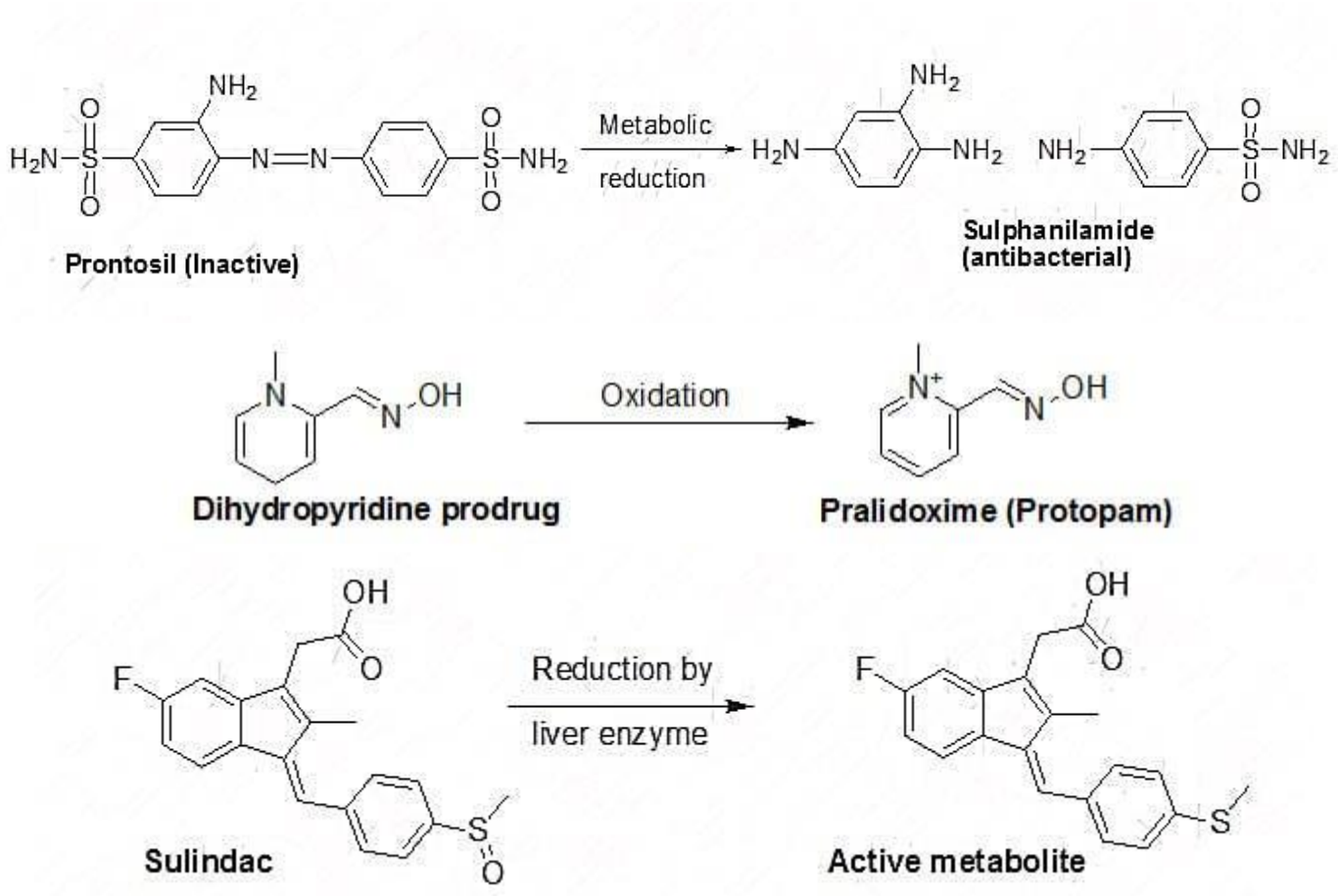
The bio-precursors are different from the carrier linked prodrug on the basis of metabolic activation they are activated by oxidation and reduction by oxidation and reduction rather than hydrolysis.

These medication based on the active principle itself. And designed from a molecule modification.

They have no carrier and do not contain a temporary linkage between the active drug and carrier moiety.

The molecule must be metabolized to undergo functional be metabolized to undergo functional group transformation for example, if a drug contains a carboxylic acid group, the bio-precursor can be a primary amine that can be metabolized first to the aldehyde and then to the acid.

EX: - nabumetone, pronslosil



There are some ideal example of bio precursor like sulindac an anti-inflammatory agent. It contains sulfoxide group. Which has activation by the reduction mechanism by liver enzymes. The sulfoxide transformed to a thither and the active metabolite generates after reduction.
It is used to treat chronic and acute inflammatory problems on the comparison it has lower concentration so, decrease GI irritation and side effects than other non-steroidal anti-inflammatory drug like ibuprofen.

Pralidoxime is the another example of bio precursor. It is used to treat poisoning organ phosphorus molecules as an antidote. It is activated through oxidation process in this pyridine group is replaced with dihydropyridine to generates a prodrug and thus enhances lipophilicity to cross the blood brain barrier because pralidoxime is very polar and unable to crosses the blood brain barrier to overcome this problem. The dihydropyridine is converted to pyridine is converted to pyridinium to give the parent drug Pralidoxime.[5]

Characteristics	Carrier prodrugs	Bio precursors
Bio activation	Hydrolytic	Oxidative or reductase
Lipophilicity	Stronger modified	Slightly modified
Catalysis	Chemical or enzymic	Only enzymatic
Constitution	Active principle 1 carrier group	No carrier

Fig.9 differences between bio-precursor and carrier prodrugs[6]

polymeric prodrug- this is the arrange in which drug mint of the drug diffused and contain the polymer (both) naturally occurring and synthetically prepared system between drug and polymer. It is also called as macromolecular prodrug.

EX: - an ideal example of macromolecular prodrug is includes p-phenylene diamine mustered is covalently attached to polyamino polymer

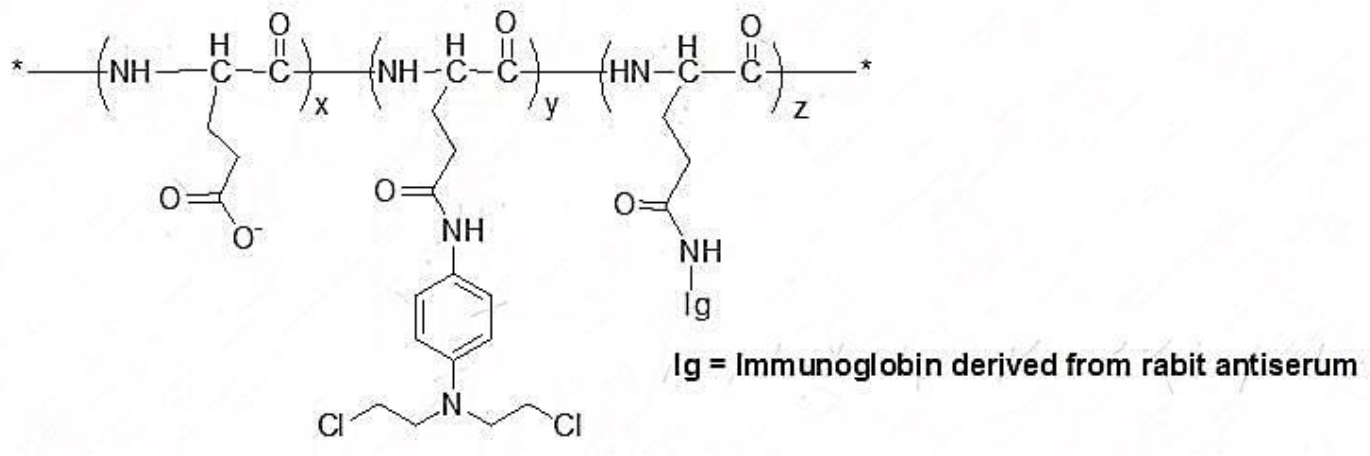


Fig.10

This poly (methacrylate chain was linked to the polymer due to an increase of water solubility it is a synthetic polymer linking & a linking of poly (methacrylate with testosterone &does not have and androgenic effect. So to overwhelm this problem an insertion of a linker between the polymer and testosterone has effects like testosterone.[5]

Classification based on the functional groups.

- Prodrugs are also classified according to the functional group, as follow:

(i) Carboxylic acids and alcohols
(ii) Amines
(iii) Azo linkages
(vi) Carbonyl compound

(i) Carboxylic acids and alcohol – prodrugs of carboxylic and alcohols functioning based on the conversion of esters. The esters can be easily hydrolyzed by esterase enzymes (e.g. lipase, ester hydrolase, cholesterol esterase, acetyl cholinesterase, and carboxy peptidase) present in plasma and other tissue to give active drugs. [6]

EX: - chloramphenicol, palmitate

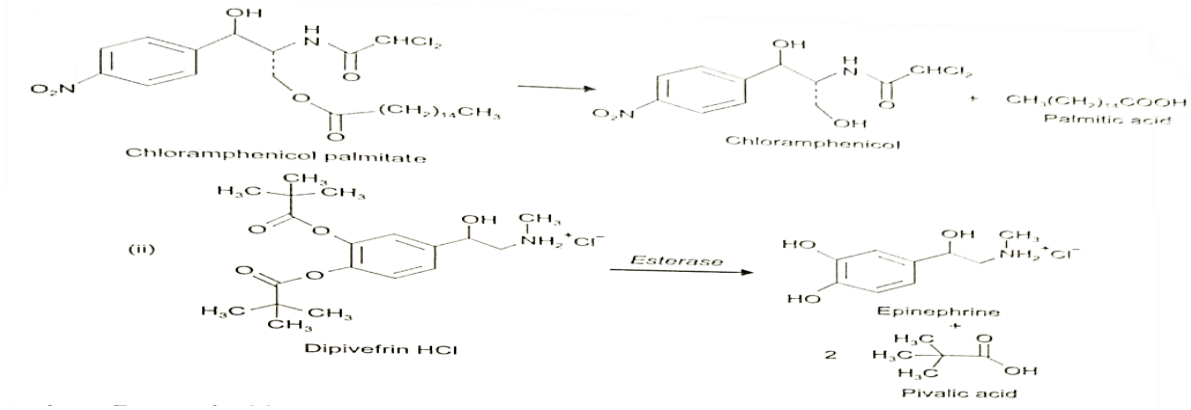


Fig.11

(ii) Amines- prodrug of amines has high stability and lack of amides enzymes necessary for hydrolysis, due to lack of conversion amides enzymes of amines to amide as a prodrugs is not been used for most

of the drug. The adaption of mannich bases as prodrug form of amines is a more common approach of amines.[6]

EX: - hetacillin is a prodrug form of ampicillin in which amide nitrogen and amino functionalities have been allowed to react with acetone to give a mannich base imidazolidine ring system. This leads to decrease in the basicity and increase in the lipophilicity and absorption.

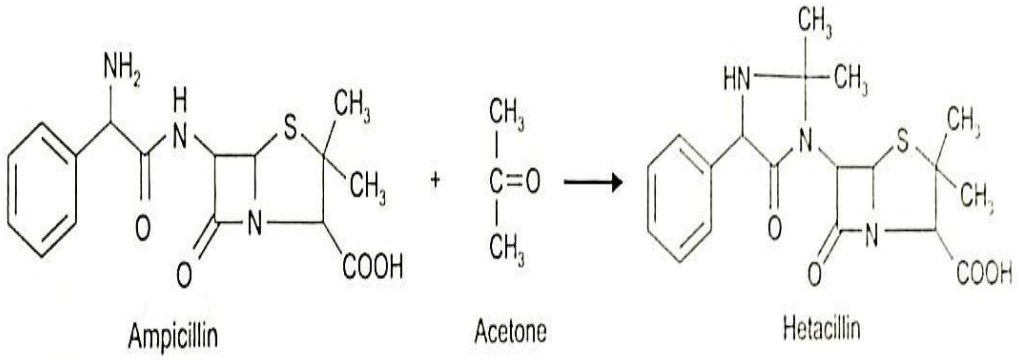


Fig.12 Hetacillin

(iii) AZO linkages- these are the prodrugs often prepared by incorporating them in to an AZO Linkages with prodrugs of amines. Conversion of prodrugs is occur by the action of AZO reductaze the amino compounds are released in vivo.[6]

EX: - prontosil drug is inactive in vitero, but it is active in vivo since it is converted to sulphanilamide by azo reductase enzymes.

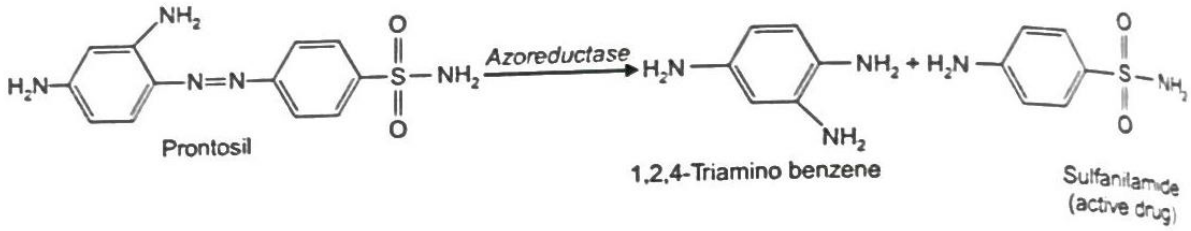


Fig.13

(iv) Carbonyl moiety- these prodrug function on the conversion of carbonyl moiety, in to aldehyde and ketone.[6]

- These prodrugs have not been found wide clinical use. The sp^2 carbonyl carbon is converted as sp^3 hybridized carbon attached to heteroatom. To form a derivatives.
- These prodrugs are re-converted to carbonyl compound by hydrolysis.[6]

EX: - Hexamine releases formaldehyde in the urine (acidic pH), which acts as an antibacterial agents.

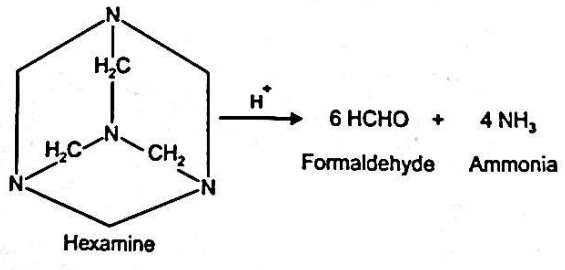


Fig.14 Hexamine

Designing prodrug using different functional group as carrier

s.no	Carriers	Name of parent drug
1	Ester	Palmarumycin, Etoposide, Diclofenac, Acyclovir, MSX-2, Cf1743, Oleanoic acid, Oridonin, Taxoids, Paclitaxel, Gambogic acid, 6-Methoxy-2-naphthylacetic acid and Quercetin
2	Amides	DW2282, Acyclovir, SB-3CT, NAP-G2-Asp, PC190723 and Pyrazolo[3,4-d]pyrimides
3	Phosphates	α-6-Chloro-2- (methylthio)-5-(napthalen-1-yloxy)-1H-benzo[d], Propofol, Lopinavir, Chalcone, SB-3CT and SNS-314
4	Carbamate	CI-994
5	Carbonate	CHS8281
6	Ether	10-Hydroxycamptothecin and Cadalene
7	Imine	Amphotericin B

Fig.15[5]

Development of prodrug

(1) Recent development in therapeutic nanoparticles based on prodrug:

Two drug design and formulation ideas that can be utilized separately or in combination to aid with some of the inherent difficulties of drug development are introduced in this article. The first is the use of a prodrug method, which highlights how chemically altering an active pharmaceutical ingredient (API) can be a flexible way to optimize the core characteristic of a drug for pharmaceutical and pharmacological benefits. This section is backed up with examples that are therapeutically applicable and show how prodrugs can be utilized to improve an API's pharmacokinetic (PK), pharmacodynamics (PD) and formulation properties as well as its toxicity profile. Additional, some of the difficulties faced in the development of prodrug are described.[7]

The main advantages of nanoparticle-based drug delivery system are then emphasized. These advantages include improved stability and bioavailability, regulated drug release and bio-distribution, improved therapeutic efficacy, and decreased toxicity. This synopsis lays the groundwork for the application of nanoparticles as vehicles to regulate the usage of prodrugs in PNDDS. Although PNDDS is a new and developing subject.[7]

Example of PNDDS products under development provide evidence in favor of the case for combining the benefits of the prodrugs and NP methods into a single product. A PNDDS's increased complexity will be tolerable, nevertheless, only if it offers substantial advantages.[7]

These may include improvement in the efficacy and safety of the prodrug through increased loading capacity, improved stability, bioavailability, or systemic exposure, or enhanced targeting and release to diseased tissue. While most examples apply to oncology indications, there is a trend towards using a combination prodrug nanoparticle strategy in other disease areas such as infectious, inflammatory, cardiovascular, neurological, and pulmonary diseases. This section emphasizes that while the emerging field of PNDDS show a lot of potential and promise, continued efforts are required to translate these new technologies from bench-to—bedside and validate PNDDS as a commercially viable drug developments strategy. Improvements in the prodrugs stability, bioavailability, or systemic exposure, as well as better targeting and release to sick tissue, may boost the prodrugs effectiveness and safety. There is a trend toward adopting a combination prodrug nanoparticle method in various disease domains, such as infectious, inflammatory, cardiovascular, neulogical, and pulmonary disorders, even though the majority of examples

relate to oncology indications. This sections underlines that while PNDDS is an emerging subject with lots of potential and promise, further work is needed to verify PNDDS as a commercially viable drug development technique and get these novel technologies from the bench to the bedside.[7]

(2). Nanoparticle-

Based drug delivery system

Since they can transport significant therapeutic drug payloads and preferentially deliver them to particular tissue or place, nanoparticle have attracted increasing interest as treatment in recent years. Cover different nanoparticle based delivery strategies, include liposomes, solid lipid nanoparticle, micelle, cub some, polymeric nanoparticle, and inorganic nanocarrier. The PK properties of their APIs may be altered by nanoparticle based drug delivery methods, potentially resulting in a longer half-life and higher distribution to the site of action, which can enhance efficacy and lessen side effects. Nanoparticle formulation can make poorly soluble hydrophobic medicines amenable for distribution by a variety of methods of administration and enhance. Their Biological availability additional, medication can be carried in nanoparticle in a synergistic molar ratio to maximize clinical efficacy or with targeting moieties to deliver drugs more precisely to the site of action. Once the nanoparticle has reached the target site, other design components are concentrated on the best release of drug target site. When temperature pH, or other physiological variable change, environmentally sensitive nanoparticle based delivery methods enable controlled or sustained drug release from the matrix.[7]

Additionally, certain inorganic nanoparticle exhibits stimuli responsive properties, such as the ability to remotely initiate the release of medicine using either an external magnetic field or their surface plasma resonance feature. The creation of nanoparticle is a process that is intrinsically complex and necessitates a thoroughly grasp of the fundamental principle that underline particle production, stability, and perform. Schematic representation of various uses are shown in and have been explored elsewhere. Although nanoparticle based drug delivery methods have been employed in clinical setting since the early 1990s, area has continued to advance alongside technological advancement to enhance therapeutic delivery. There has been a thorough analysis of the development and advancement of clinically authorized nanoparticle based drug delivery system that contained unaltered pharmaceutical. The difficulties and prospects for these platform will be the main topic in this section.[7]

(2.1) Difficulties and direction for the future:

Nanoparticle technologies can be advantages, but there is still a poor success rate for clinical translation. Some difficulties. The challenges that nanoparticle based delivery system still have to overcome include the need for even greater control of drug release kinetics and bio distribution, as well as enhancement to formulation qualities like stability and encapsulation efficacy. In one instance, SPI-77, a cisplatin-encapsulating long- circulation liposome that is currently undergoing clinical studies was due to the encapsulated drug's sluggish and ineffective release. A second illustration. The clinical efficacy of L-NDPP (AroplatinTM), a cisplatin analog (cis-bis-neodecanoato-Trans-R, -1,2-diaminocyclohexane platinum II) contained within nonPEGylated multilamellar liposome, was limited by undesirable accumulation in the liver. Additionally, after reconstition, there were significant amounts of complex degradation, which rendered the medication inactive. LiPlaCis, a brand new liposomal formulation of cisplatin with triggered release capability, serves as another illustration. It is intended to be broken down by secretory phospholipase A2 in tumor areas. Acute infusion reaction due to renal toxicity were seen in a lot of patients, but poor safety profile indicates that additional reformulation and optimization are needed. In order to provide optimum pharmacology and toxicity profiles, it is necessary to better understand how biology affects Nano carrier PK. Plasma proteins in vivo absorption on nanoparticle can change the by that nanoparticle interact with biomolecules, changing their pharmacological.[7]

Characteristics, therapeutic efficacy, and toxicity, which helps explain by in vitro and in-vivo results don't always correlate. This mechanism known as protein corona (or bio corona) creations is perhaps the most important one influencing how nanoparticle behave and end up when given intravenously. The clinical translational potential of the formulation may also be hampered by their structural and physicochemical

complexity because it can be difficult to pharmaceutically produce complicated nanoparticle system on a big scale. Overcoming insufficient batch-to-batch consistency and stability, low product output, inadequate quality control and product purity, and other specific issues and expensive. However, the therapeutic potential of nanoparticle drug delivery system is encouraging, and as these existing constraints are overcome, the case for their significant impact on human health will get stronger.[7]

(3) Prodrug formulation in nanoparticle is progressing:

Two major approaches were discussed in the portion of this review that comes before them for enhancing the PK, safety profile, and therapeutic efficacy of medicines. The first involve directly altering an API chemically to create a prodrug, while the second involves encapsulating medicines inside of Nano carriers. Despite the benefits listed in both tactics have obstacles to overcome, as discussed in the preceding section. Prodrug lack of protection may cause them to clear quickly and degrade prematurely, while nanoparticle based delivery system may experience poor drug loading and leakage. Combining these two approaches enables formulation scientists to have more influence over the chemical and biology characteristics of treatments and may improve clinical translation. For instance, the degradation of prodrugs can be reduced with the protection of Nano carriers to explore different administration methods. Improved efficacy can be attained by changing the nanoparticle surface chemistry. This section reviews a number of PNDDS articles from 2018 or later, showing their potential benefits over prodrug or nanoparticle only approaches.[7]

(3) Oncology

Many candidates are in the clinical developments stage, even though there is only one PNDDS that is now approved without a doubt, oncology has produced the most prodrug based nanoparticle formulation that is being used in clinical setting. This is perhaps because more acceptable cancer treatment are so desperately needed. These attempts are discussed needed. These attempts are discussed in numerous publications, many of which have also been examined elsewhere. Here, API has compiled a list of the most recent PNDDS for the treatment of cancer.[7]

(3.3.1) Platinum based substance

Despite a number of serious drawbacks, platinum based medication is among the most effective chemotherapeutics now on the market. The main ones are medication resistance brought on by in effective cellular intake, glutathione (GSH) inactivation, and metallothionein detoxification, as well as dose limiting adverse effects. There have been numerous attempts to create innovation platinum based therapies that reduce toxicity and boost therapeutic efficacy in order to address these limitation. One such is a collection of prodrug based on platinum that are redox responsive and have various hydrophobic carboxylate ligands (designated as pt(IV)n). The hydrophobic prodrug self-assembled to generates a pt(IV) n prodrug based nanoparticle delivery system (Pn NP) for cancer therapy when the Pt(IV) n prodrugs are combined with amphiphilic lipid PEG. The lead formulation that results from endocytosis and exposure to intracellular GSH exhausting impact, which lowers the likelihood of thiol- medicated platinum detoxification. Longer blood circulation and more tumor accumulation in vivo were caused by the nanoparticle PEG functionalization. In vivo tumor xenograft mice mode, our PEGylated P6 NP delivery platform produced improved treatment. Using carboxylate from PEG poly (glutamic acid) block copolymers, NC 6004, also known as nanoplatin, is a micellar nanoparticle formulation. The platinum metal center of this type of Pt medication is cross-linked to block co-polymers by co-ordination bond, forming labile bond that enables it to be categorized as prodrug and causes micelles to self-assemble. In a variety can cancer animal model, nanoplatin was more well tolerated than cisplatin and provide more antitumor efficacy. Nanoplatin and gemcitabine were able to obtain to higher cisplatin equivalent doses in a phase IB/II clinical trials in patient with advanced solid tumors without experiencing clinically relevant toxicity problems, indicating the possibility of a wider therapeutic window.[7]

Using several formulations and a similar design method, DACH-Pt, 1,2-diaminocyclohexane platinum II, a platinum based prodrug, was examined as a possible treatment for recurrent ovarian cancer. These formulation, a copolymer that lengthens plasma half-life a chelator that bind inactive platinum spaces at physiological pH to prevent of target effects are commonly used. The active platinum spaces is released to

achieve to targeted delivery after being exposed to low pH environment present I tumor. For nanoparticle production to occur, the platinum the species must be chelated the most sophisticated formulation, known as ProLinDac or AP5346, contains and amidomalonato chelator and a hydroxypropylmethacryamide (HPMA) copolymer and was both secure and affective in a phase II clinical trials. Recently the DACH-Pt prodrug was reformulated as part of a self-assembled bio-degradable dendritic copolymer based drug delivery system (NP-TPGS-Pt) treatment for lungs cancer that multi drug resistant. Pt metal center and a-tocopheryl PEG 1000 polymer unit were chelated by carboxylate moieties that were provided by the conjugation of a PAMAM-MH2-G3 dendrimer to glutamic acid in this study. NP-TPGS-Pt formulation inhibited the development of drug resistant. A unique approach to treating tumors that are resistant to many drugs is to treat cancer cell in vivo.[7]

(3.1.2) Camptothecin

Camptothecin is another frequently used chemotherapeutic medication. Since its discovery, a great deal of research has concentration on creating novel camptothecin analog in an effort to increase its water solubility and anticancer activity. Irinotecan and topotecan, two camptothecin analog, have been authorized for use in cancer treatment. In response, treatment the prodrug irinotecan, which is converted tonits active metabolite SN- 38 by non-specific carboxylesterases, is the most extensively studied of these. Irinotecan has a number of negative clinical effects, including rapid drug clearance and significant dose- limiting toxicities such neutropenia and diarrhea. By preventing irinotecan from being metabolized too soon, a carefully thought-out drug delivery system might provide a ways to get around these restrictions. One such system is the liposomal formulation of irinotecan, which was created for the treatment of metastatic pancreatic cancer. It was given in conjunction with 5-fluorouracil and leucovorin and was authorized by the FDA in 2015. It is intended for patients who have previously received gemcitabine treatment. The combination of onivyde/5-flurouracil/leucovorin maintained its overall survival benefits in the phase III NAPoli-1 study. Compared to 5-fluorouracil/leucovorin treatment alone, the 12-month follow up and a sufficient safety and tolerability profile were both positive. Onivyde is only allowed for use in conjunction with 5-flurouracil/leucovorin because monotherapy did not exhibit greater efficacy compared to the treatment with 5-fluorouracil/leucovorin and was linked to more adverse events than combination therapy.[7]

Additionally, a phase I/II open- label (NCTO2551991) is currently being conducted to examine the safety, tolerability, and dose- limiting toxicities of onivyde when used as a first-line therapy for people with metastatic pancreatic cancer. This trial compares onivyde with 5-flurouracil, leucovorin, and oxaliplatin. By addressing the drawback of anticancer single-drug treatment, this extra onivyde combination therapy is a prospective method to enhance the clinical outcome for the treatment of a number of tumor types. As was previously discussed in the prodrug section of this review article, this example used the prodrug irinotecan to deliver the active metabolite SN-38 as part of a liposomal formulation. However, other prodrug design strategies can be envisioned for virtually any active compound through modification of the labile bond type and the pro-moiety structure. To administer SN-38, researchers have created alternate prodrug/nanoparticle delivery methods.[7]

Example of a redox- responsive lipophilic SN-38 prodrug, hydrophobic SN-38 redox hypersensitive Nano rods, and SN-38 grafted amphiphilic phosphorylcholine polymers.[7]

One further camptothecin analog is 10-hydroxcamptothecin (HCPT), which is more potent and less poisonous than camptothecin. However, due to its poor water solubility and chemical instability, which is caused by the opening of its labile lactone ring at physiological pH, HCPT cannot be used in clinical settings on a large scale. Different Nano medicines have been created to assist HCPT in achieving more efficacies with lesser toxicity.[7]

The most recent invention was a phenylboronic acid pinacol ester Nano carrier that responds to ROS and is loaded with a guanidine-modified HCPT prodrug (HCPT-Gu). By applying a pre-formed poly (L-glutamic acid)-g- methoxy PEG (PLG-g-mPEG) nanoparticle to a hyper- branched aliphatic polyester (HAPE) using steglich esterification, PLG-g-mPEG-HAPE (PgP-HA) was created. In terms of stability and drug loading capacity, the PgpHA Nano carriers for the drug HCPT-Gu displayed very good performance. Due to hydrophobic contacts, stacking interaction between the phenylboronic acid pinacol ester group of PgP-HA

and the HCPT prodrug, and the superposition of hydrogen bonds from the guanidine and carboxyl groups.[7]

Due to guanidine's potential for cell penetration, in vitro uptake experiment revealed that HCPT-Gu enhanced cellular uptake in comparison to HCPT alone. PgP-HA/HCPT-Gu nanoparticles exhibited a longer circulation time than HCPT-Gu alone, according to in vivo PK studies, suggesting a higher capacity to reach and maintain high amounts of drug at the target tumor location. PgP-Ha-/HCPT-Gu nanoparticle demonstrated an 80.6% growth inhibition rate with little toxicity in vivo antitumor effectiveness studies, which is consistent with the better PK profile. However, while having a moderate level of systemic toxicity, HCPT and HCPT-Gu only significantly decreased tumor growth by 27.4% and 34.6%, respectively. The potential of PNDDS manufacture for the development for the development of cancer therapy is overall shown in this study.[7]

(3.1.3) Etoposide

As a targeted treatment for a variety of tumor types, glycoside prodrug like etoposide have been created. However, their use has been constrained by the prodrug's complicated production and poor in vivo API modification. A ketal glycoside prodrug was created to overcome these problems.[7]

Recently developed to release its active metabolite after exposure to both glycosidase enzymes and low pH conditions. The ketal glycoside etoposide (ETP) prodrug was created but conjugating hydroxyl group containing monosaccharaides with hydroxyl group containing ETP using pH sensitive acetone based ketal linkages. By means of Nano precipitation, the resultant amphiphilic ketal glycoside prodrug were subsequently self- assembled into nanoparticles coated with glucose. The prodrug made using this approach demonstrated glycosidase and acid triggered self immolative hydrolysis, as evidenced by hydrolysis experiment that revealed the ketal glycoside prodrug exclusively released native ETP and glucose.[7]

(2)

Due to the overexpression of glucose transporters in A549 cells , which are lung cancer cells, these prodrug Nano particles showed substantial cellular accumulation , indicating that this technique . The prodrug nanoparticles were also demonstrated to preferentially concentrate in tumors in mouse model of an A549 xenograft using a combination of the EPR effect and uptake mediated by glucose transporter binding. compared to other organs , tumor tissue experienced more hydrolysis because to the tumor cells' acidic , high - glycosidase environment .with no toxicity , the prodrugs adorned with glucose as immunotherapies or as a starting point for the creation of stimulus - responsive self - immolating prodrugs for targeted chemotherapy.[7]

(3.1.4) Gemcitabine:

Nucleoside analog gemcitabine is used to treat various cancers. However, early metabolism, negative PK, and off - target action have made it difficult to utilize in clinical settings. Numerous prodrug techniques have been investigated by conjugating gemcitabine with long fatty acids to overcome these problems chains of squalenic acid. Recently, pH-sensitive gemcitabine polyketal prodrug nanoparticles were created with the intention of boosting anticancer activity not only by lengthening systemic circulation time but also by attaining effective gemcitabine accumulation at the humor site. The prodrug in this study was created by coupling gemcitabine to a polyketal backbone using pH - sensitive ketal linkages, followed by the encapsulating of the Nano precipitation. During in vitro drug release tests, prodrug nanoparticles showed sustained release of the active metabolite in pH- dependent manner. In comparison to free gemcitabine, improved anticancer effects were shown in the A2780 ovarian cancer cell line in a xenograft mice model, leading to higher survival rates and improved tolerability. This study shows that pH - sensitive polyketal prodrugs have the potential to enhance the anticancer and antiviral activity of diol nucleoside analogues.[7]

(3.1.5). Dual - drug treatment

The dual - drug cocktail approach has been widely employed in cancer therapies to overcome drug resistance , boost overall therapeutic impact, and decrease side effects brought on by the requirement for

higher doses when providing the same medications individually. To the contrary, in clinical settings, co-delivery PK difference between various medications might result in decreased efficacy, which makes it challenging to combine different drugs. Two medications are delivered simultaneously in one co-delivery approach, which has recently gained attention due to its advantages over free drug cocktail -based delivery regimens. Here are various PNDDS that combine numerous APIs, either as covalently linked codrugs or with at least one being prodrug, to offer a more promising method of chemotherapy. About 15%of all breast cancer cases are known to have triple negative breast cancer (TNBC), which is characterized by tumors that lack the cellular expression of the estrogen receptors (ER) and progesterone receptors (PR). Additionally, they do not overexpress the HER2 protein on the surface. These triple negative tumors are more aggressive and have prognoses because they do not respond well to hormone - targeted therapies like tamoxifen (TAM) or HER2 - targeted therapy. Interestingly, several investigations have demonstrated that histone DE acetylation contributes to the suppression of ER gene expression, and as a result, the use of histone deacetylase (HDAC) inhibitors can restore the expression, and as a result, the use of functional ER. In order to put this strategy into action, the first pan-HDAC inhibitor licensed by the FDA for use in various tumors was vorinosat (suberoylanilide hydroxamic acid, SAHA).studies have revealed that SAHA resnsitzed TAM-resistant cells to hormone therapy and (that SAHA improved TAM efficacy when dosed in conjunction with TAM. (TAM\SAHA) does face some significant obstacles, while combination therapy are SAHA's poor stability, limited oral bioavailability, and insufficient distribution of the two medicines to the tumor sites. To overcome these constraints, scholars have a SAHA prodrug - based nanoparticle delivery system was created to co-deliver SAHA and TAM for more successful combo therapy. Reversible addition-fragmentation transfer polymerization was used to create the polymeric prodrug, POEG-co-PVDSAHA, which contains SAHA. Using disulfide bonds that are redox-responsive, polymer. In this design, SAHA participates in the hydrophobic domain of the amphiphilic polymer, facilitating the production of stable micelles as well as TAM encapsulation. The resulting TAMloaded POEG-co-PVDSHA micelles shown increased and synergistic cytotoxicity against TNBC cell lines in comparison to free SAHA, free TAM, and a combination of the two. The use of structure-transformable co-drug-based nanoparticle technology is another method to increase TNBC's sensitivity to cisplatin. Based on cisplatin and adjudging (ADD), a group of self-assembled co-drugs known as Pt (IV) - ADD were created. The Pt (IV) - ADD co-drug can work synergistically to cause cell death due to the different modes of action of these medicines, mitochondria dependent apoptosis and DNA damage. In terms of nanoparticle production, Pt (IV)-ADD and 1,2- distearoyl-sn-glycero-3-phosphoethano lamine-PEG (DSPE-PEG)'s amphiphilic nature self-assembled, uniform Nano- formulations [Pt (IV) - ADD-@PEG NPs] with high drug loading. A dynamic equilibrium between ADD and the conjugated carbon allowed one of the resulting NP formulations, C24-PtADD@PEG NP, to change into aware structure upon IV administration. Chains, signifying its morphology's thermodynamic stability. In comparison to free cisplatin and the non-transformable formulations, C4-Pt-ADD@PEG NPs had improved therapeutic efficacy in cisplatin-sensitive and cisplatin-resistant cell lines. Higher drug retention at the tumor site and stronger tumor inhibition were seen in mice with MDA -MB-231 tumors that were resistant to cisplatin, which may indicate related to the secondary structural rearrangement, which may promote drug retention, as well as the synergistic impact of ADD and cisplatin. Together, this structure - transformable nanoparticle and combination therapy have the potential to further the fight against TNBCs. Another example of co-drug nanoparticle-based combination therapy used a lipid-PLGA nanoparticle to carry out a two-in-one co-delivery design. In this case, cisplatin hydrate and tolfenamic acid (Tolf), a highly selective COX-2 inhibitor, coordinated to create the co- drug (Tolfplatin). Lipid- PLGA@ Tolfplatin nanoparticles (LPTP NPs) were created as a result of an inhibitor that decreased the polarity of cisplatin by linking it to the extremely hydrophobic Tolf. Cisplatin hydrate destroys DNA, whereas Tolf increases p53 expression, are the two active ingredients that use separate methods of action to cause apoptosis. When cisplatin hydrate and Tolf were released following intracellular endocytosis in a breast tumor-bearing animal model, the LPTP NPs passively localized to and aggregated at the tumor site via EPR effect of anticancer impact that works together. This co-drug-based nanoparticle delivery method showed superior tumor accumulation and increased therapeutic efficacy in comparison to free cisplatin, free Tolf, and the combination of two free cisplatin, free Tolf, and the combination of the two free medicines. It also showed no off-target tissue damage.[7]

(4.2) Other indications:

PNDDS have been studied in different indications, diseases including infectious inflammatory, cardiovascular, neurological, and pulmonary illnesses, even though oncology has received the greatest attention to them.[7]

(4.2.1). Including infectious diseases:

Infectious disorders caused by bacteria and viruses have both been treated with a small number of PNDDS. For instance, sofosbuvir was adsorbed onto amino-decorated mesoporous silica nanoparticles, a proTide-type prodrug authorized for the treatment of hepatitis C. When sofosbuvir was administered using a nanoparticle vehicle as opposed to not, a rat PK investigation revealed that plasma exposure of drug doubled and the time to C tripled. In addition, the surface functionalization of the nanoparticle using either polyvinyl alcohol (PVA) or 3-aminopropyltriethoxysilane (APTES) could be used to regulate the drug release profile.[7]

For example, the APTES coating of mesoporous silica nanoparticles showed an initial burst release of around 30% of the sofosbuvir in the first hour, followed by a steady release of the remaining sofosbuvir over the course of 16 hours. In contrast, the PVA- coated particles showed an initial release of 10% or so of sofosbuvir in the first hour, followed by a rapid release of up to 85% of sofosbuvir after four hours; it should be noted that for PVA - coated particles, 100% release was not obtained. These results show once more that altering the nanoparticles structure can affect drug delivery and that oftentimes, fine- tuning the entire formulation is necessary to achieve the desired qualities.[7]

For the prodrug tenofovir alafenamide, which was also covered in the prodrug section of this review articles and is optimized for improved cell uptake in anti-HIV combination therapy, formulations a drug delivery system may further enhance outcomes for groups at high risk of HIV infections by boosting compliance. Using pre- exposure prophylactic treatment. Because of numerous administration occasions or the flexible nature of the recommended dose regimens, compliance is frequently hampered. Recent research by Mandal et al., who created a long - acting release formulation encasing the antiHIV prodrug combination therapy tenofivir alafenamide\emtricitabine (TAF\FTC) inside pluronic F-127 and PLGA-based nanoparticles, provides one example of a treatment that may increase adherence.[7]

The nanoparticles Formulation’s half - life at the site of infection in vaginal tissue was at least 6.5 Times longer than that of TAF/FTC medication solution, and its AUC was three to five times greater. When administered 7 or 14 days prior to the viral challenge, the controlled release nanoparticles was found to be 60% more effective in preventing infection than the free medication control group at preventing infection in humanized mouse model of HIV. These findings taken together imply that a nanoparticle- based strategy may allow for a decrease in the dose frequency of pre-prophylaxis medication, which could significantly impact compliance and treatment results.[7]

A “shock and kill" therapy strategy has been thoroughly investigated in order to circumvent the virus's defense mechanism within latent reservoirs. With the help of cytotoxicity drugs that are specific to HIV-1 cells or immune - mediated clearance, this technique uses latency- reversing agents (LRAs) to trigger viral replication area of the infection. This strategy is still debatable has had made mixed results in clinical settings, which can be related to poor drug concentration at the target locations, insufficient LRA immunotherapy potency, off-target toxicity, or nonspecific T cell activation. An appealing approach to overcoming these difficulties would be the use of delivery systems based on nanoparticles.[7]

Lipid-coated PLGA hybrid nanoparticles (LCNPs) were coated al.to enable the co-delivery of different LRAs (JQ1, DSF, Ing3A, cholesterol butyrate (chol-but), prostratin, and panobinostat, or PANO) were physically encapsulated and added to the (4.2.1). Including infectious diseases: LCNPs. (Ing3A- PLGA, PRs- PLGA, and PANO- PLGA), Chemical conjugation to PLGA with either an ester or amide bond (JQ1/LCNP, DSF/ Ing3A- PLGA, Prs- PLGA, and PANO - PLGA), Chemical conjugation to PLGA with either an ester or amide bond (JQ1, /LCNP, DSF / LCNP, Ing3A- LCNP,) insertion into the lipid bilayer (chol-but LCNP), or any combination of these methods. In addition, self- assembly into LRA-loaded LCNPs (such as Ing3A-LCNP,) insertion into the lipid bilayer (chol-but LCNP), or any combination of these methods. In addition, self - assembly into LRA - loaded LCNPs (such as Ing3A-LCNP, Prs- LCNPs as

compared to free LRAs or physically enclosed LRAs, reducing the unintended first burst release. In the J-Lat Tat-GFP cell line model, all LRA - LCNPs shown cytoxicity that was either equal to or less toxic than the free drug, indicating that LCNPs could give greater dosages for improved efficacy while minimizing toxicity. The optimum choice was found to be the combination of Ing3A-LCNP and JQL/LCNP, which displayed synergistic latency reversal with minimal cytotoxicity, balancing the tradeoff between toxicity, potency, and synergy.[7]

Additionally, treatment with his combination enhanced HIV-1 mRNA expression levels in CD4 T cells from infected people who were being kept on suppressive highly active antiretroviral therapy in a synergistic manner. The Ing3A - LCNPs accumulated in lymph nodes following subcutaneous treatment and specifically coupled to and activated CD4 T cells in mice by incorporating CD4 antibodies on the surfaces of LCNPs as the active targeting motif. Although additional research is still required to fully assess the latency reactivation in a non-human primate simian immunodeficiency virus model, the encouraging results of this young field for discovering an HIV cure.[7]

Nitric oxide (NO) - releasing polymers and NO- prodrugs that are polymer - encapsulated are being researched for the treatment of bacterial infections. By damaging DNA, inactivating metabolic enzymes, and decreasing the strength of the bactericidal activity without the risk of antimicrobial resistance beginning to arise. The therapeutic efficacy of this strategy, however, faces difficulties because to the non- specific nature of special interest in tackling this problem. In one study, NO caused bacterial biofilms to break apart at Pico molar and Nano molar concentrations, resulting in planktonic germs that became resistant to antibiotic therapy. Making use of this effect, Nguyen et al. generated combined NO and antibiotics micelles by directly conjugating a NO-donor (Ndiazeniumdiolate (NONOate)) to a gentamicin - decorated amphiphilc block copolymer of poly [(oligoethylene glycol) methyl ether methacrylate] and 3- vinylbenzyladehyde (POEGMA - b - PVBA) to form 15nm diameter particles. In vitro treatment of biofilm mass compared to minor reductions after treatment with free gentamicin alone, NO- donor alone, micelles. Similar results were seen when assessing biofilm viability, indicating that a dispersing agent can be helpful in boosting the effectiveness of conventional antibiotic medications against biofilm - associated infections.[7]

(4.2.2).Inflammatory diseases:

Inflammatory conditions including arthritis have also been studied in relation to PNDDS treatment. Drugs are physically encased in non - prodrug nanoparticles- based delivery systems including polymeric micelles and protein nanoparticles, however one drawback is that these systems frequently burst release. Behavior low drug loading or both. Therefore implementing cutting - edge prodrug techniques to enhance the design of the delivery systems can aid in increasing their clinical translations. Modular pH-sensitive acetone - based ketal linked prodrugs of dexamethasone (AKP- dexs) were developed by Xu et al and made into nanoparticles to treat rheumatoid arthritis [301]. Eight AKP - Dexs with various chain lengths were created and co- assembled into nanoparticles with DSPE - mPEG200, an amphiphilc polymer. Long- carbon- chain alcohols were more effective as pro-moieties because they. The ability to create stable nanoparticles with excellent encapsulation efficiency is made possible by the compatibility of dexamethasone with DSPE-mPEG2000. The AKP-dex-loaded nanoparticles displayed increase accumulation in arthritic joints as well as efficient dexamethasone release in a rat model of collagen- included arthritis. Compared to the free water soluble prodrug, dexamethasone sodium phosphate, the arthritic joints' micro environmental is acidic. This study reveals that pH- sensitive prodrug nanoparticles may offer an appealing platform for their increased therapeutic efficacy and minimal systematic adverse effects.[7]

For example: polymeric micelles containing diclofenac are another example of a PNDDS that may be used to treat inflammatory illnesses. Some of the most frequently given treatments for pain and inflammation are non-steroidal anti-inflammatory drugs like diclofenac.

They do, however, have a number of negative effects, including increased cardiovascular to the level of drug present in the heart. By reducing diclofenac's distribution to the heart. AI- Lawati et al. demonstrated that administration with polymeric micelles lowered the cardiovascular hazards of diclofenac.[7]

In this study, traceable polymeric micelles (DFEE-TM) were created utilizing a solvent evaporation technique by mixing diclofenac ethyl ester with the block copolymer PEO-b-PCL conjugated with the near - infrared probe cyanine -5.5 azide. After a single IV injection, increased fluorescence levels were seen in the inflamed joints of adjuvant arthritis (AA). rats compared to the joints of healthy rats in ex vivo near infrared optical whole- body imaging, indicating that the DFEE - TM were localized in the inflamed areas due in part to the inflammation to the PEO's long term characteristics. In addition, after seven daily doses of DFEE -TM compared to dosing with free diclofenac, in the hearts of AA rats was significantly decreased. An important cardio toxicity indicator was decreased in the heart and plasma of AA rats, which is consistent with this finding. By modifying their biodistrubution and improving their accumulation in the permeable vasculature of the subject, this study proved that prodrug - incorporating polymeric micelles can lessen the toxicity of conventional medicines.[7]

(4.2.3) Cardiovascular diseases:

A PNDDS with potential for use in cardiovascular therapy is a thrombus - targeting aspirin particle for the management of thrombotic sickness. Ethyl salicylate (ESA; aspirin) had been designed In this study as polymer - drug conjugate (APP) which was then combined with the anti- coagulant and anti-inflammatory drug APP was combined with fibrin - binding peptide Gly- Pro- Arg - Pro - Pro (GPRPP) - lipid conjugates, DSPE -PEG-GPRPP, via H202 - scavenging per oxalate linkages to create thrombus - targeting aspirin polyconjugate particles (T - APP) with anti - inflammatory and anti – coagulant characteristics. When evaluated in H202 - stimulated arterial endothelial cells, release of ESA from T- APP resulted in a decrease in observed H202 which means that intracellular ROS . When T- APP was tested in a mouse model of blood vessel thrombosis and tail bleeding, it was discovered that treatment with TAPP caused the bleeding time to rise by almost two times when compared to treatment with free aspirin, indicating a stronger anti - thrombotic impact . T- APP was also strongly connected to a synthetic thrombus after IV injection in a rat model of carotid artery thrombosis. This result was eliminated once the. To prevent T- APP binding, free fibrin - targeting GPRPP - peptide has been given to animals previously.[7]

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These studies point to a promising new use for aspirin in the treatment of serious blood clots in the body, in addition to T-APP’s strong anti-inflammatory properties. To maximize the therapeutic effects of FDA-approved prodrug like lovastatin, nanoparticle made of chitosan and alginate have also been used. The active hydroxyl acid form of the cholesterol lowering prodrug lovastatin is hydrolyzed in vivo and inhibits 3-hydroxy-3-methylglutaryl-Coenzyme a reeducates that affects the manufacture of cholesterol. However, because of its short half-life (about three hours), evening administration is needed, which decreases patient compliance and limits its use. In order to regulate the release of a drug called and establish a good absorption and distribution profile, lovastatin encapsulating alginate/chitosan nanoparticle were created in this study. The structure and shape of the nanoparticles are controlled by interaction between the polymer and lovastatin in the final formulation (ACL nanoparticles), which occur through hydrogen bonding and dipolar-dipolar interactions. ACL nanoparticles released lovastatin more quickly and at a higher rate when combined with increasing the pH of a solution. For the first 10 hours, the release was quick (80%-90%), and then the remaining 10-20% came out slowly for up to 30 hours. In studies of acute and sub chronic toxicity following oral treatment to healthy mice, the ACL nanoparticles were also found to be harmless. Due to their controlled release characteristic, these finding show that ACI nanoparticle could be used to improve the pharmacological action of lovastatin.[7]

(4.2.4) Neurological disease:

Neurological problems have also been treated using a combined prodrug nanoparticle method. A prodrug of dopamine, the FDA-approved Parkinson’s drug, is described in the prodrug section. Levodopa (L-DOPA), a medicine, has good BBB absorption. The gastrointestinal tract and system circulation, however, quickly breaks down it. While many more dopamine prodrugs are being developed to address this problem, the use of Nano carrier to protect levodopa from serum decarboxylase activity while effectively crossing the BBB and concentrating on the brain gives a new method. Gonzalez-carter et al. produced L-DOPA-AuNFs, which have been functionalized with the targeting ligand L-DOPA, as potential brain- penetrating delivery method.

They showed that, against that which has been reported in the literature, more L-DOPA-AuNFs travelled across the brain using an in vitro human BBB model (hcMEC/D3 cell line).[7]

Additionally, their transportation rate across the BBB monolayer was equivalent to that seen in monolayer made of cells from the outside of the human umbilical vein. In vitro, brain macrophages internalized L-DOPPA-AuNFs highly without causing overt inflammation. These positive outcome offer hope for changes in the treatment of brain disease, even if the pharmacological value of these prodrug-loaded gold nanoparticles has not been tested.[7]

(4.2.5) Pulmonary diseases:

Pulmonary disorder may potentially benefit from PNDDS as a kind of treatment. As an example, pulmonary arterial hypertension (PAH), a progressive condition identified by increased pulmonary arterial pressure carried on by occulted and/or limits pulmonary vasculature, occurs despite a number of approved treatments.[7]

The 5 year survival rate is still low for PAH treatment. Numerous PAH medications already in use are also liked to negative side effects induced on by systemic exposure. One of three prostacyclin analogues that have been approved to treat analogues that have been approved to treat PAH is the vasodilator treprostinil, which comes in the form of an oral tablets (Orenitram), a solution for inhalation (tyvaso), and a continuous infusion (Remodeling). While the nebulized tyvaso formulation enables local API delivery to the lung, it takes four daily doses and is associated with significant negative effects brought on by systemic exposure. One or three prostacyclin analogues that have been regulated to treat PAH is the vasodilator treprostinil, which comes in the forms of an oral tablets (Orenitram), a solution for inhalation (Tyvaso), and a continue infusion (remodeling). Even though. The tyvaso formulation delivered of the API to lungs; however, it required four doses per day and is linked to local side effects such coughing and sore throats. A novel treprostinil based nanoparticles formulation was created and is currently undergoing clinical testing to treat PAH in order to address these drawbacks.[7]

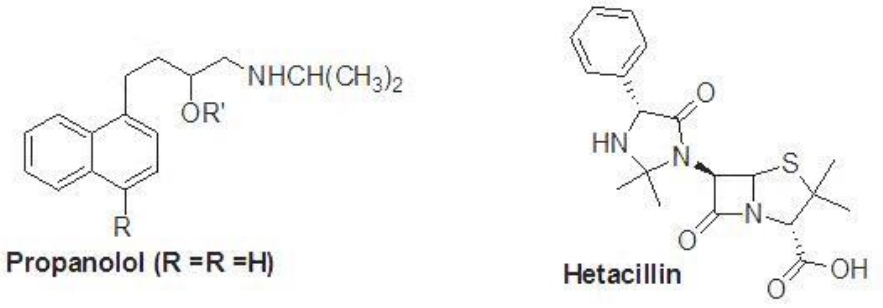
Treprstinil palmitil is a prodrug that combines palmitil alcohol as the pro-moiety and an ester link to conceal the carboxylic acid functional group of treprostinil acid, leading to a significant altered solubility profile and decreased water solubility.[7]

The clinical components of the treprostinil acid API and treprostinil palmitil prodrug. A lipid nanoparticle made of squalane and DSPE-PES2000 can contain the prodrug because of its improved lipophilicity. The squalane functions as a hydrophobic filler, and the “stealth” coting provide by the DSPE-PEG2000 enhances formulation stability and decrease prodrug discharge.[7]

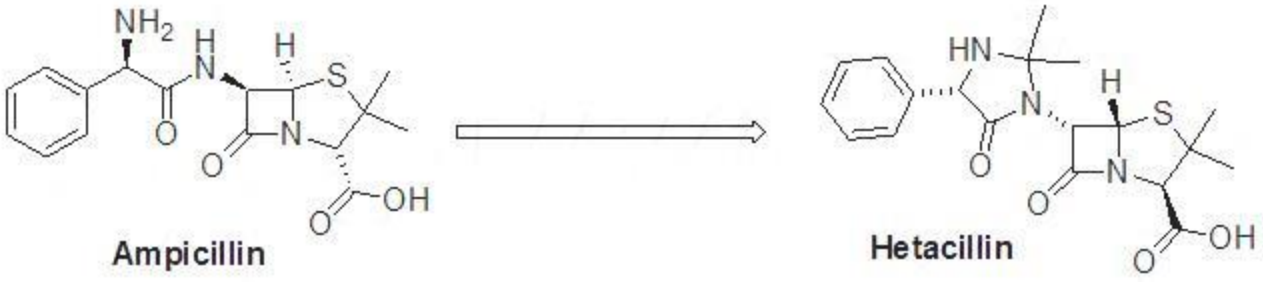
Why the prodrugs are used:

(A) Improved chemical consistency:

Every medicinal agent needs to maintain its chemistry. The prodrug technique, as stated above, depends on changing the functionality responsible for the unstable character. This technique aims to alter the drug's physical properties as well, which reduces the drug's ability to interact with the media. Propranolol, for instance, is used as an antihypertensive medication (Figure 27, R = R' = H). An oral dose has a lower bioavailability than an intravenous injection dose due to first-pass exclusion of the medication. The three main metabolites of this medication are p-hydroxy propranolol (Figure 27, R = OH, R' =H), propranolol, and its O-glucuronide synthesis. The plasma levels of propranolol can be eight times higher when propranolol hemi succinate is taken orally as compared to when propranolol is used.[5]

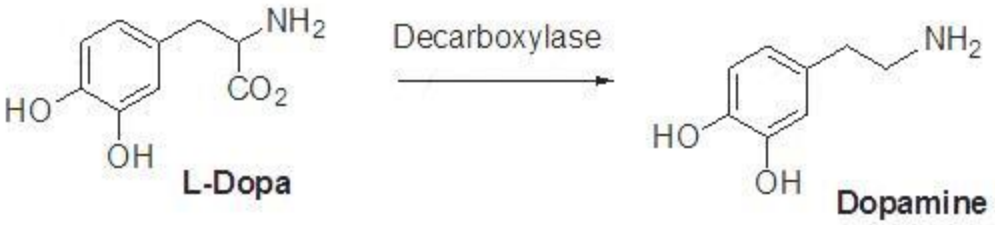


A member of the beta-lactam antibiotic family is hetacillin. This prodrug has no antibacterial properties; however it can convert acetone into the antibiotic ampicillin in the body. The Ampicillin produces polymeric species by preventing auto-aminolysis, which is made possible by the NH2 group's ability to connect to the other molecules -lactam structure. A prodrug of ampicillin binds up the amino functionality and inhibits auto-aminolysis by forming hetacillin.[5]

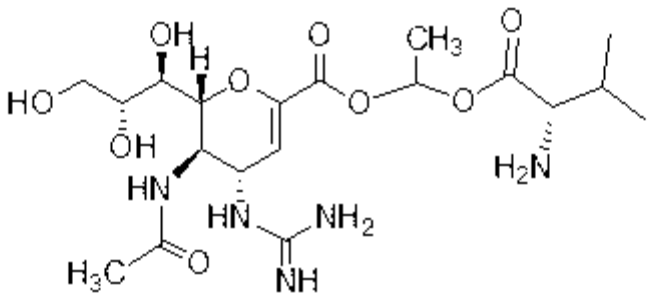


(B) Improvement of bioavailability:

The gastrointestinal absorption of multiple drugs, including vitamins, natural purine and pyrimidine nucleosides, dopamine, ampicillin and carbenicillin, phenytoin, and GI toxin, is poor. These chemicals' weak lipophilicity, polarity, and metabolic tendency are the main causes of their weak immersion. The thiolate ion is treated to create a fat-soluble prodrug, which enhances the absorption of vitamins. The medical benefits of dopamine are achieved by L-Dopa, its precursor. A polar molecule is L-dopa. This is transmitted by the L-amino acid active transport process and dopamine is reborn via a decarboxylation pathway.[5]

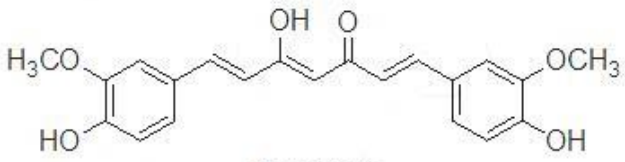


A prodrug of zanamivir called L-valyl zanamivir has been created. Through the PepT transporters, this prodrug is more easily absorbed. Its oral absorption can be improves by this procedure.[5]

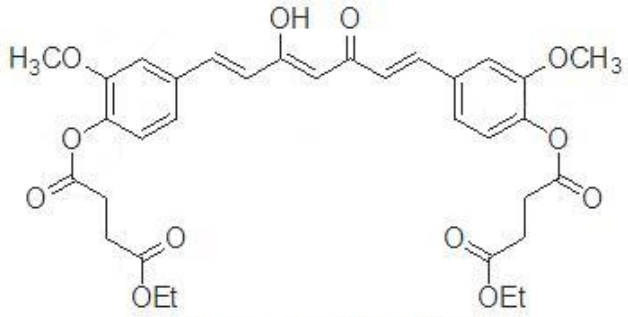


Chemical structure of L-valyl zanamivir.

Because it is unstable under physiological settings, cur cumin has a low bioavailability. Due to poor absorption and a fast metabolism, it exits the body. The bioavailability of cur cumin has been improved using a variety of techniques that solve problems. Diacids, amino acids, and glucose are conjugated. This process appears in.[5]



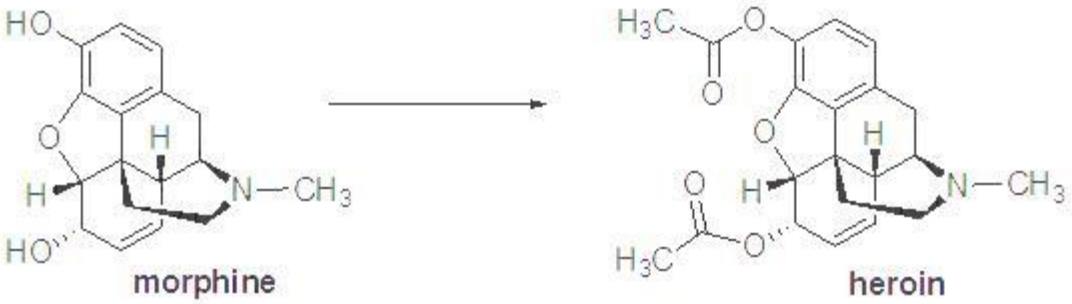
Curcumin



Curcuminoid prodrug

(C) Preventing presystemic metabolism:

A successful drug should pass using the liver and digestive system before reaching the transmission. Many medications can be metabolized through oxidative N- and O-DE alkylation, ester hydrolysis, or peptide breaking. The stomach's acid swiftly breaks down the first category of medications. The liver and digestive mucosa's enzymatic processes break down the second group of medicines. If a specific capability is safeguarded by derivatization, the metabolism of the medication is blocked. The drug's physicochemical properties can also be changed. For example, naltrexone, an opioid addiction treatment drug, is rapidly absorbed in the digestive tract and undergoes presystemic metabolism.[5]

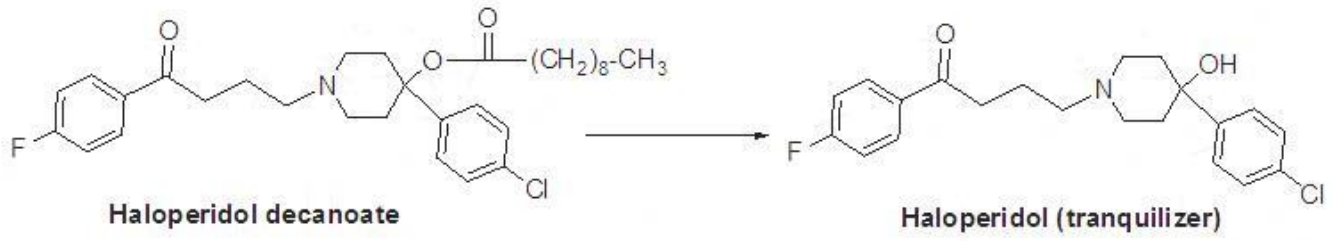


morphine heroin

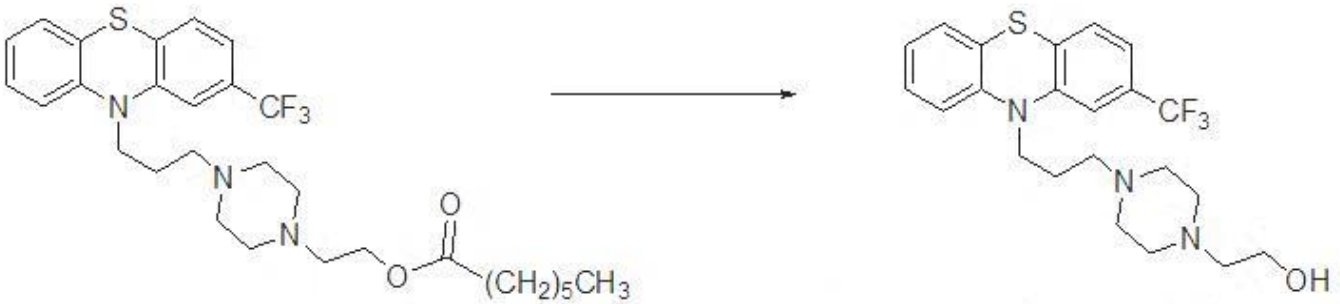
(D) Presystemic metabolism extension:

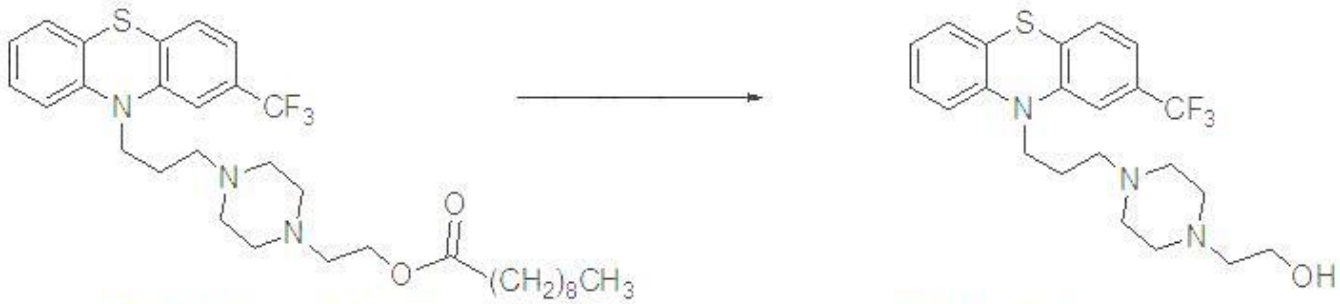
The activity duration of a drug can be maintained by the prodrug if a medication has a short half-life period and is administered frequently with an equal dosage. Prodrugs like testosterone propionate, estradiol propionate, and fluphenazine deaconate have the respective active substances of testosterone, estradiol, and fluphenazine as the main components.[5]

Drugs with a prolonged half-life are essential for treating psychosis. This group's patients need their medications for a longer period of time. The maximal plasma level of the sedative and tranquilizer haloperidol is observed 2 to 6 hours after intake. If administered intramuscularly, the prodrug haloperidol deconate remain active for one month.[5]

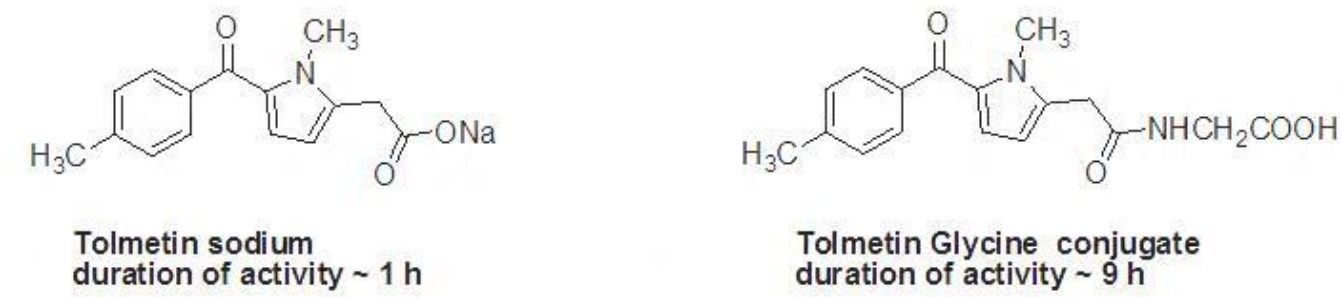


Antipsychotic medication's effect lasts for 6–8 hours, but fluphenazine's activity lasts for a month.





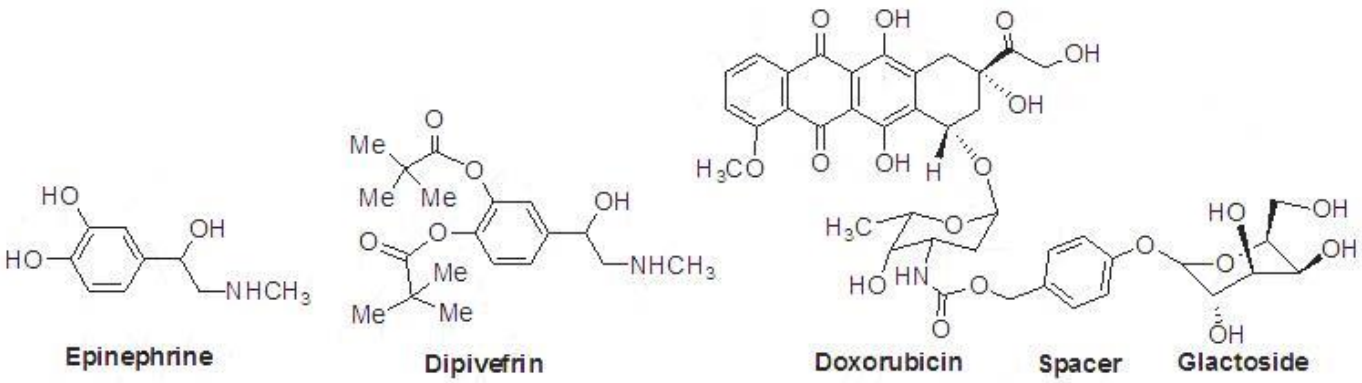
Tolmetin sodium, an anti-inflammatory medication, is changed into a glycine conjugate to improve action and extend its highest concentration to about 9 hours. the prodrug amide bond's weak hydrolysis can result in this.[5]



(E) Decrease in toxicity:

Prodrug toxicity should be minimal or absent. Eye medication epinephrine causes numerous ocular and systemic adverse effects. Prodrug dipivaloyl epinephrine has a better profile and is more active than

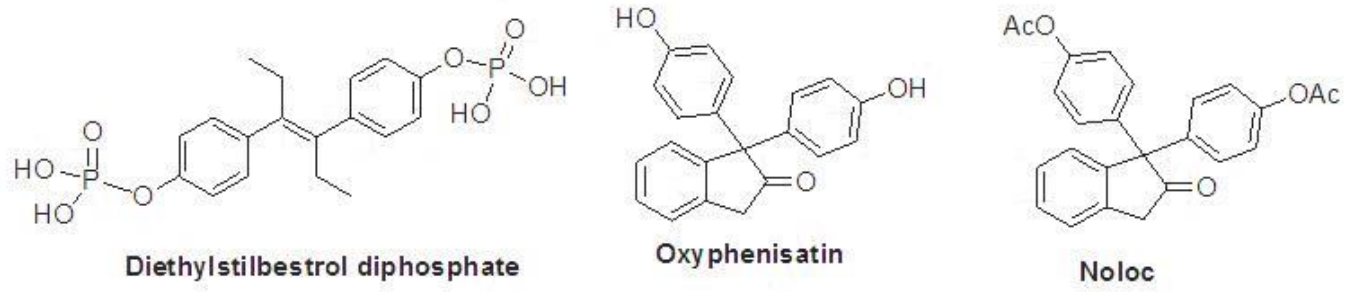
epinephrin. Doxorubicin is a cancer-fighting medication. However, due to its cardio toxicity, this medication must be used with caution. Designing medications that would boost doxorubicin availability in cancer cells but minimizing its effects on heart function was significant. To do this, a galactoside prodrug with doxorubicin and a carbamate group was created.[5]



The negative effects of sulindac are much less than those of indomethacin and it has no impact on the stomach. A diisobutyrate ester of terbutaline used to treat glaucoma is called ibuterol. Number 38 This prodrug is 100 times stronger, takes up to three times as long, and doesn't have any local or systemic side effects.[5]

(F) Particular delivery to the site:

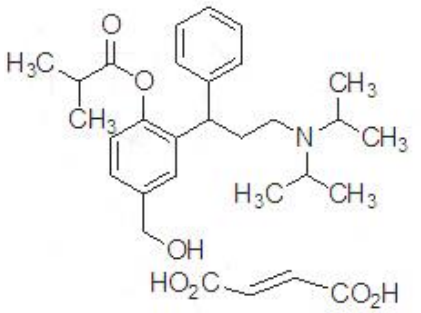
If the physicochemical properties of the original drug and the prodrug are suitable with the target site, the targeting of medications to the internal organs using conversion to a prodrug works well. Different body parts are targeted by the medications. By prodrug-designing the medication to target the actual source of the issues, this constraint is overcome. After that, the target tissue undergoes the prodrugs conversion to the drug's active form. Specific enzymes or acidity can cause this process to happen. Phosphate and amides are present in higher concentrations in tumor cells than normal cells. If these enzymes are needed for the prodrug to be activated, a cytotoxic prodrug is then administered to the tumor cells. For the site-specific administration of diethylstilbestrol to patients with prostate cancer, diethylstilbestrol di-phosphate has been developed. Given rectally, oxyphenisatin is a bowel sterilant. Oxyphenistatin acetate, an acetylated prodrug, is taken orally. Finally, it is converted to oxyphenisatin at the digestive level.[5]



(G) Structures, applications, and use of a few prodrugs with FDA approval from 2008 to 2018 [80–89]:

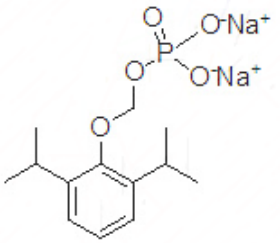
• Fesoterodine Fumarate:

To obtain the active substance, 5-hydroxymethyl tolterodine, esterase hydrolyzes the prodrug fesoterodine fumarate (trade name: Toviaz). It helps to use a muscarinic receptor antagonist to treat hyperactive bladder muscles that cause problems with frequency, urgency, and leaking.[5]



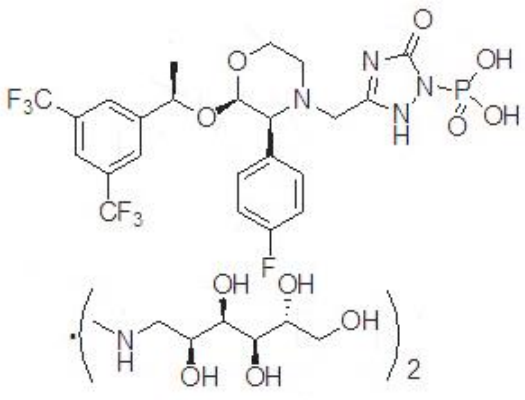
• Fospropofol disodium:

Alkaline phosphatase transforms the prodrug fospropofol disodium (which is marketed as Lusedra) into its active component, propofol. An intravenous sedative-hypnotic drug called fospropofol, which is frequently given as disodium injection, is advised for adult patients having supervised local anesthesia care sedation, such as endoscopy.[5]



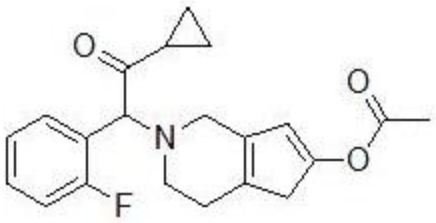
• Fosaprepitant dimeglumine:

The prodrug fosaprepitant dimeglumine, also known as Emend, is activated by phosphatase-catalyzed DE phosphorylation to produce the substance that acts aprepitant. In chemotherapy regimens, fosaprepitant dimeglumine is used together with other antiemetics to minimize both early and delayed nausea and vomiting following the application of some cancer chemotherapy treatments.[5]



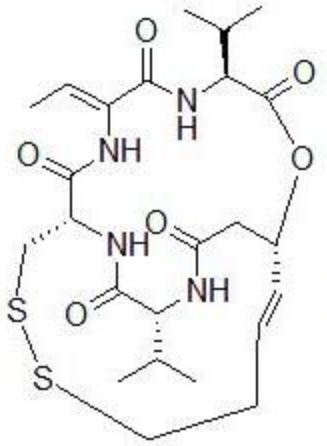
• Prasugrel:

The prodrug of prasugrel (brand name: Effient) decreases by esterase and CYP450 metabolism to produce the active drug, R-138727. Patients with acute coronary syndrome with heart disease who have a specific heart operation as well as those with specific heart or blood vessel changes take prasugrel in combination with aspirin to prevent blood clots.[5]



• Romidepsin Prasugrel:

Intracellular glutathione activates the prodrug romidepsin prasugrel (trade name Istodax), resulting in the production of the drug's active metabolite, which has a free thiol group. An injection of romidepsin, an HDAC inhibitor, should be considered for the treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy and at least one other form of treatment.[5]



Application of prodrugs:

In most situations, the objective of pro -drug development is to address certain pharmaceutics, pharmacological, and pharmacokinetic issues. The following are the primary objective of pro -drum:(8)

- Taste improvement
- Odor improvement
- Bioavailability is improved
- improvement to the qualities of stability and solubility
- Decreased toxicity and negative effects
- Enhanced site specificity
- Increase duration of pharmaceutical effect
- Pharmacokinetics is affected by drug absorption, distribution, metabolism, and excretion.

Taste improvement

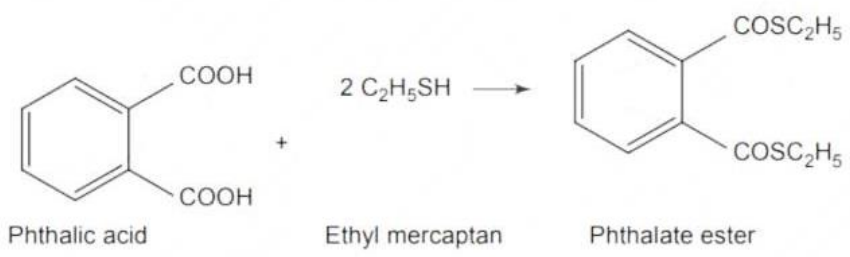
The bitterness, acidity, or causticity of the medicine is one of the factors contributing to low patient compliance, particularly in children. The foul taste of the medication is addressed using two methods. The bitterness is marked by the first strategy, which reduces the drug's solubility in saliva, and the second involves lowering the drug's a few example of medication with enhanced flyover.

Table Of Drugs With Improved Taste

Parent drug	Pro-drug with improved taste
Chloramphenicol	Palmitate ester
Clindamycin	Palmitate ester
Sulfisoxazole	Acetyl ester
Erythromycin	Estolate

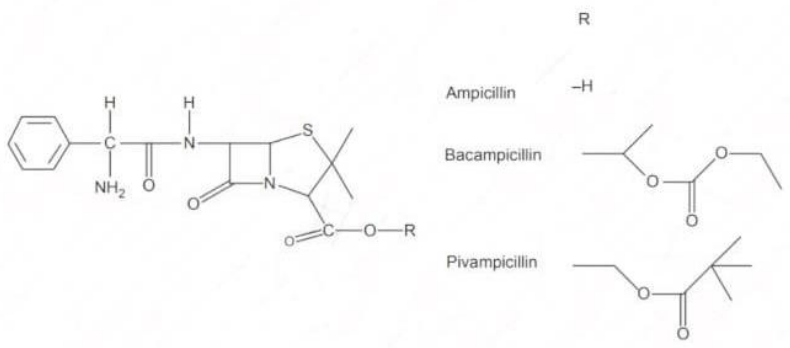
Oder improvement

The vapor pressure of a substance affects its smell; a liquid with a high vapour pressure will have a strong smell. Ethyl mercaptan, for instance, is a leprosy therapy that uses a foul – smelling liquid. A diethyl dithioisophthalate with a higher boiling point and no Oder is created when this is converted to phthalate ester.



Bioavailability is improvement

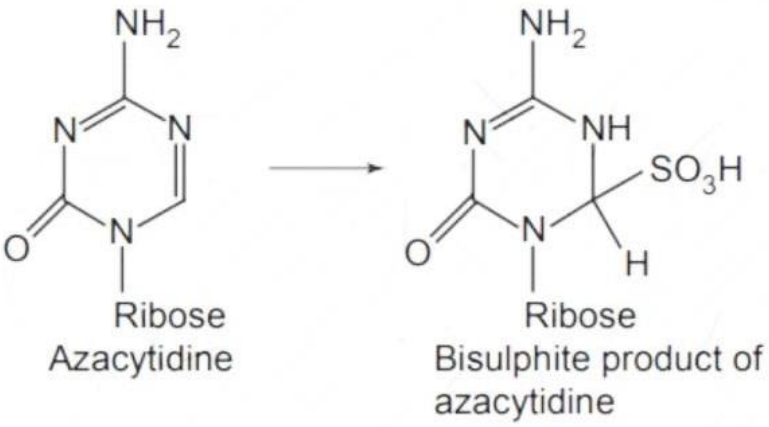
Ampicillin has a low lipophilicity and is only 30% -40% absorbed when taken orally since chain contain an amino groups .By esterifying the free carboxy group , this antibiotic 's polarity can be changed , resulting in compounds that are more bioavailable than the parent ampicillin because they are entirely absorbed.



Improvement to the qualities of stability and solubility

Stability: The prodrug method is a useful technique to increase their stability. When taken orally, a no. of medications can decrease during their shelf life or in the gastro intestinal tract [GLT]. Azacytidine easily in an acidic pH, although its bisulphite prodrug is more stable. Solubility: In order to formulate such

medication for parenteral or ophthalmic use, hydrophilic or water – soluble compound are required. By using half ester like hemi – glutarate or hemi -phthalates, which carry sodium, potassium, or amine ions on their other half and make the moiety soluble, drugs having hydroxyl functional groups can be transformed into their hydrophilic form.



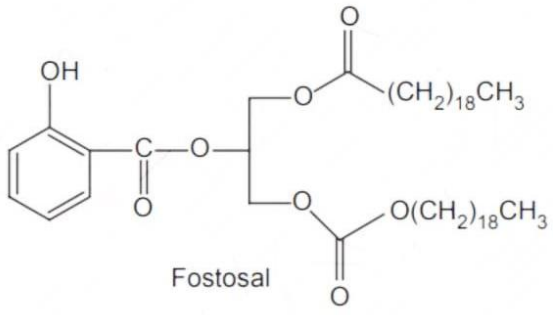
Azacytidine

Bisulphite product of azacytidine

Parent drug	Pro-drug with enchanced hydrophilicity
Tocophenols	Sodium succinate ester
Metronidazole	Amino acid esters

Decreased toxicity and negative effects

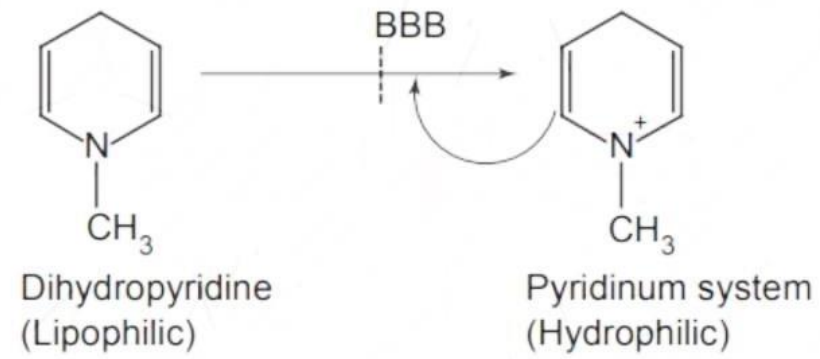
In some case, phenols and carboxylic acids are too harmful to be used in therapeutic setting. The absence of stomach ulcer genic activity in ester prodrugs of acidic non-steroidal anti-inflammatory drugs is thoughts to be one of the causes of these medication negative side effects.



Fostosal

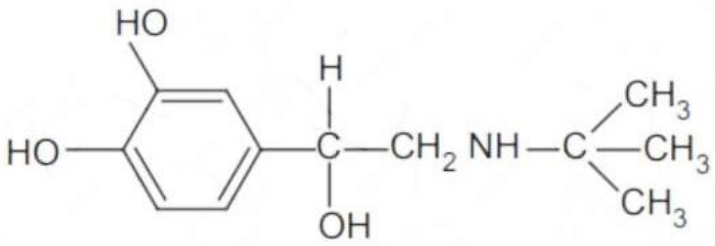
Enhanced site specificity

Many pro-drugs may be designed in such a way that they are only toxic to certain organs when they are administered to a chemical to the brain, the dihydropyridine / pyridinium redox system is particularly useful.



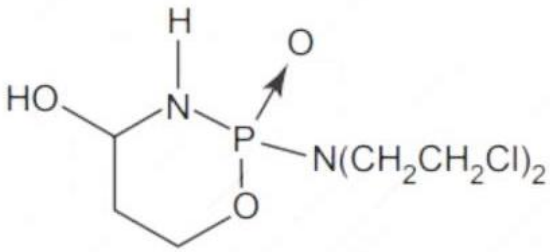
Increase duration of pharmaceutical effects

N-butyl noradrenaline‘s pro-drug di-p-toluate ester gives bronchodilator activity that lasts longer then the parents medication. The bronchodilator action is produced because the pro-drug is preferentially transported into the lung tissues compared to the plasma or the heart.



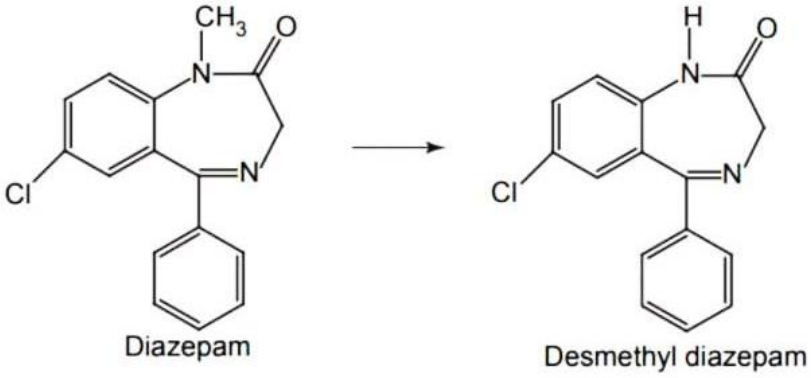
 # BIO-PRECURSOR PRODRUG

In place of a carrier or a promoiety, a bio-precursor pro-drug includes a latent the ability that is converted into an active drug molecule though metabolic or chemical processes. The types of phase I activation include chemical activation oxidation, reduction, and phosphorylation.

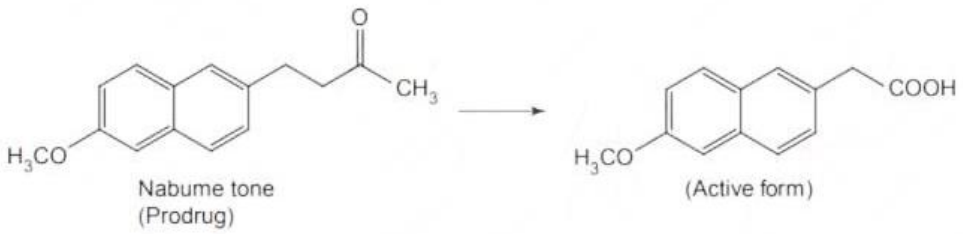


Bio – activities: The pro-drug is transformed into the cytotoxic phosphoxamide mustard by cyclophosphamide‘s breakdown.

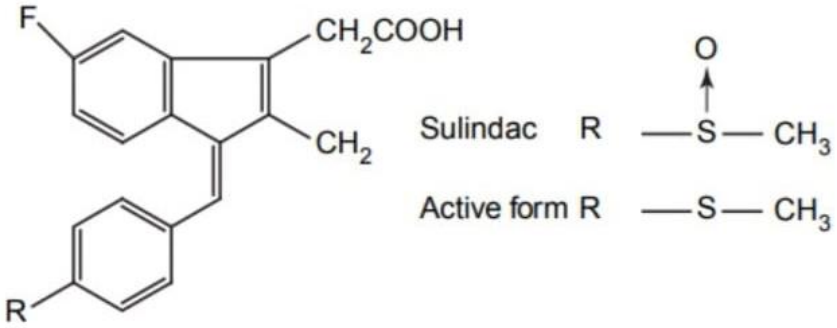
N-DE alkylation: This chemical process changes several drug into their active metabolites form.



Oxidation: The prodrug nabumetone, in which the formyl groups was generated, a carboxylate group is formed, resulting in the production of the active substance.



Reduction: sulindac is converted in vivo from its nonsteroidal anti - inflammatory drug form to its active form.



Conclusion

In this chapter we have completer prodrugs about prodrugs, what is prodrug & history of prodrugs,, ideal properties of prodrugs, the purpose of designing prodrugs, classification of prodrugs, development of prodrugs, uses of prodrugs and application of prodrugs. These all topics are important for prodrugs. These all topics are important for prodrugs information and used for better formulation to inhance safety, stability and other parameters.

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