**PRO-DRUG DEVELOPMENTS**

Rathore Urmila1, Gupta Ravikant1, Vengurlekar Sudha1

1. University Institute of Pharmacy (UIP), Oriental University, Indore (M.P.)

**Abstract:**

The design and development of pro-drug is grounded on the purpose to ameliorate the pharmacokinetic and pharmacodynamics profiles. A admired number of pro-drug have been reached the medicines request throughout history and the recent times have witnessed a significant increase in the use of pro-drugs as a relief of their parent medicines for an effective treatment of colorful ailment. At present, the pro-drug approach is dragged with conjugating the parent medicine with a tone- offering patch or linker which itself assembles into nanoparticles and dragged the blood rotation and having unresistant targeting capability. It also includes delivery of the medicine at target point having specific pH condition, delivery of medicine to brain, pro-drug with sustained release. Receptor targeted, binary action pro-drug, and activation via specific enzyme. Some other approaches toprol-drug development are the conversion of active pharmaceutical constituents ( API) into ionic liquids. In addition to enhancement in combination chemotherapy. The Pro-drug approach has shown numerous successes and still remains a feasible and effective approach to deliver new active agents.

The prodrug conception is a veritably useful approach for the optimization of ADMET( immersion, distribution, metabolism, excretion, and toxin) parcels of pharmacologically active halves to increase their application by cases and to increase the bioavailability of these pharmacologically active halves. The physicochemical, natural, and organoleptic parcels of the medicine substances can be modified to increase the remedial efficacity, reduce toxin, and increase patient compliance. Although prodrugs have the advantages of prostrating issues associated with parent medicines, they've been considered to have lower remedial exertion than the parent medicine. The prodrug must release active medicine and cross-linked promoiety before, during, after immersion, or within specific target towel depending upon the purpose of prodrug strategy. currently, a prodrug methodology is considered the most favorable point-specific medicine delivery strategy that's applied to deliver a medicine substance to a target point or target organ. presently we distinguish in remedy traditional prodrugs prepared by chemical derivatization, bio precursors and targeted delivery systems. The present composition is a review regarding the preface and operations of prodrug design in colorful areas of medicine development.

**Keywords:** Aqueous solubility, lipid solubility, classification of prodrugs, drug development, optimization of bioavailability

# Abbreviations

ADME Absorption, Distribution, Metabolism and Excretion. QSAR Quantitative Structure Activity Relationship

HLB Hydrophilic Lipophilic Balance

ADEPT Antibody-directed enzyme prodrug therapy VDEPT Virus-direct enzyme prodrug therapy GDEPT Genedirected enzyme prodrug therapy CYP Cytochrome P450

GI Gastro Intestinal.

NSAIDs Non-steroidal Anti-inflammatory Drugs PEG Polyethylene glycol

QM Quantum Mechanics

MM Molecular Mechanics.

DFT Diffused Functional Theory . HF Hartree-Fock

IGAC Intramolecular General Acid Catalysis . GAC General Acid Catalysis

 EM Effective Molarity

**Introduction:**

# Preface Pro-drugs are biologically inactive composites that are actuated post-administration to their pharmacologically active forms. Frequently pro-drugs are formulated to overcome pharmacokinetic walls similar as poor solubility and immersion, expansive first- pass metabolism, or rapid-fire excretion, and pharmacodynamic walls similar as toxin, side goods, and poor efficacity. The activation of pro-drugs is generally via either enzymatic processes similar as that by cytochrome enzymes, esterases and amidases or chemical processes(interorintra-molecular) similar as hydrolysis and oxidation. numerous prodrugs have enjoyed clinical success in treating colorful habitual and acute conditions Although the product of natural treatments similar as monoclonal antibodies is considered as a promising strategy to construct new drugs, the prodrug approach is still being explored and new prodrugs are still being developed. still, recent clinical trials reflect the future of prodrugs as new treatments, corridor of concerted treatment rules, or treatments for new suggestions other than their formerly approved bones. Pro-drug might alter the towel distribution, efficacity, and toxin of parent medicine. Below are some reasons why pro-drug approach should be used in medicine design

#  ● bettered waterless solubility.

# ● bettered immersion and distribution

#  ● point particularity

# ● bettered stability of medicines

# ● For dragged release

#  ● To reduce toxin

#  ● In poor case adequacy

# ● In expression problems.

# Concept of Pro-drug

#  The abecedarian principle of the prodrug is to annihilate undesirable parcels of medicine- suchlike low waterless solubility, low lipid solubility, poor target selectivity, undesirable taste, low chemical stability, presystemic metabolism and to mask vexation upon original administration etc. The term prodrug was first introduced by Adrein Albert in 1958, according to Adrein Albert prodrug is biologically inactive outgrowth of parent medicine which undergoes chemical and enzymatic transformations in the body to release biologically active parent medicine. The prodrug conception has been used to ameliorate undesirable parcels of medicines since the late 19th century, but it was only at the end of the 1950s that the factual term “ prod- hairpiece ” was introduced for the first time by Adrien Albert for medicines that are inactive by themselves but which form an active outgrowth by biotransformation. The conception was completed by Harper in 1959 which introduced the term of medicine latentiation pertaining to medicines that were specifically designed to bear bioactivation. Prodrugs are inactive derivations of active substances with optimized physicochemical parcels( advanced stability, bettered solubility or increased permeability), that suffer a biotransformation in the body whereby are plying their pharmacological action. Prodrugs can be defined also to be drugs which have specific defensive groups, in order to help unwanted parcels of the parent patch. In utmost cases, prodrugs are simple chemical derivations that are only one or two chemical or enzymatic way down from the active parent medicine. The conception of prodrug has to be discerned from medicines that are active on their own, but by biotransformation are forming one or further active metabolites and the natural effect occurs as a common result of the original medicine and metabolites. These medicines are “ limited ” prodrugs

# The purpose of designing prodrugs

1.perfecting bioavailability when the medicine seeker isn't medicine- like due to inimical physical parcels as

 • poor water solubility,

 • low lipophilicity,

 • chemical insecurity,

 • inferior taste or smell,

 • original vexation, pain.

2.perfecting bioavailability when the medicine seeker isn't medicine- suchlike, due to pharmacokinetic parcels

 • low bioavailability,

 • poor penetration through natural membranes,

 • increased first- pass metabolism,

 • slow immersion by parenteral route,

 • rapid-fire immersion/ elimination rather of long- continuing effect,

 • lack of particularity in certain apkins. The specific ideal of prodrug design is to optimize inimical physicochemical parcels, to increase chemical and/ or metabolic stability, to achieve planned delivery.

**Classification of Prodrugs based on pharmacological action**

Prodrugs are a class of inactive or less active compounds that are pharmacologically inactive on their own but can undergo specific chemical or enzymatic reactions in the body to be converted into active drugs. The purpose of prodrugs is to improve various pharmaceutical properties of the active drug, such as enhancing its solubility, stability, bioavailability, or targeting specific tissues or organs. Prodrug classification can be based on various criteria, and here are some common ways to categorize them:

Type of Activation:

a. Enzymatic prodrugs: These are prodrugs that require specific enzymes present in the body to undergo conversion to the active drug. For example, codeine is a prodrug that is metabolized into morphine by an enzyme called CYP2D6.

b. Chemical prodrugs: These are prodrugs that undergo chemical reactions in the body, such as hydrolysis, to release the active drug. An example is acetylsalicylic acid (aspirin), which is rapidly hydrolyzed to salicylic acid in the body.

Site of Activation:

a. Tissue-specific prodrugs: These prodrugs are designed to be activated only in specific target tissues or cells, reducing systemic side effects. This can involve targeting specific enzymes present in those tissues.

b. Organ-specific prodrugs: Similar to tissue-specific prodrugs, these prodrugs are designed to be activated only in specific organs.

c. Cell-specific prodrugs: In this category, the prodrugs are engineered to be activated only in specific types of cells, such as cancer cells.

Mechanism of Activation:

a. Bio-reversible prodrugs: Prodrugs that can be reversed back to the parent drug once the desired effect is achieved.

b. Bio-irreversible prodrugs: These prodrugs convert irreversibly into the active drug once the activation process begins.

Purpose of Prodrug Design:

a. Enhancement of bioavailability: Prodrugs are designed to improve the absorption and distribution of the active drug, thereby increasing its bioavailability.

b. Enhancement of stability: Prodrugs can be formulated to protect the active drug from degradation or chemical reactions, increasing its shelf life.

c. Masking undesirable properties: Some prodrugs are designed to mask the unpleasant taste or odor of the active drug.

d. Targeted drug delivery: Prodrugs can be engineered to deliver the active drug selectively to specific tissues or cells.

It's important to note that prodrugs should be designed carefully to ensure they are safe and effective in achieving their intended therapeutic goals. Their activation should be predictable and well-controlled to avoid unexpected side effects.

**Classification of Prodrugs based on structure of the drug**

The prodrugs are classified into colorful orders as follows

* Carrier- linked Prodrugs
* Bioprecursors
* Macromolecular Prodrugs
* Spacer or Linker Prodrugs
* **Carrier- Linked Prodrugs**

A carrier- linked prodrug is a complex that comprises an active medicine which is temporarily attached to some carrier with covalent relation. The carrier group can be detached enzymatically. After administration to the body, the prodrug undergoes biotransformations and converted to the active emulsion. The ideal carrier should have following parcels. It should save the medicine until it reaches the point of remedial action. Confine the medicine at the point of remedial action.Allow the emancipation of the medicine by chemical or enzymatic action. It should bear biochemical idleness. To be fluently prepared and inexpensively. It should be inert and stable.

**Carrier- linked prodrugs are farther classified as**

* Dual Prodrugs
* Triplex Prodrugs
* Mutual Prodrugs

Dual Prodrug A dual prodrug is a prodrug comprised of one carrier linked to the parent medicine. The exemplifications of dual prodrugs are Prednisolone sodium phospha. triplex Prodrugs In triplex prodrug, a carrier is associated to the linker which is farther attached to the medicine. For illustration, Prodrug of ampicillin in which the carrier is pivalic acid and linker **is – CH2-** collective Prodrug or Co-drug Inco-drug approach two pharmacologically active composites are combined and both acts as promoieties for each other. collective prodrugs may be of both types dual or triplex. The carrier in collective prodrug may have the same remedial action as that of parent medicine or it may have some different remedial action which isn't shown by parent medicine. For illustration, a collective prodrug of sulbactam and ampicillin( Sultamicillin) is bears further advanced pharmacokinetic parcels as compared to alone parent medicines.

**Carrier linked prodrug**

Enhancement of the bioavailability and the biomembrane passage. The biomembrane passage of a medicine depends primarily on its physicochemical parcels and especially on its partition measure. therefore the flash attachment of a lipophilic carrier group to an active principle can give better bioavailability, substantially by easing cell- membrane crossing by unresistant prolixity.

**Derivatization of medicines containing alcoholic or phenolic hydroxy groups.**

Dipivaloyl- epinephrine for examplecrosses the cornea and is used in the treatment of glaucoma. Esterification of hydroxylic functions with poly- acids(e.g. succinic acid, phosphoric acid) represents an excellent way to prepare water-answerable prodrugs. Esters are readily synthesized from an alcohol- containing parent dr ug and a carboxylic acid( or acid halide or anhydride) Esters are fluently hydrolyzed by colorful and ubiquitous esterases. As a result, it's fairly easy to alter the water solubility and accordingly, immersion and distribution may also be effected as asked.

**Derivatization of medicines containing a carboxylic acid function:**

Lipophilic prodrugs can also be deduced from a carboxylic function, the most generally used derivations being carboxylic esters. Simple esters of aliphatic alcohols are seductive as they're cheap to prepare, chemically stable, and yield inoffensive hydrolysis products. Typical representatives of similar prodrugs are tyrosine methyl ester, levodopa ethyl ester etc. Esters are fluently hydrolyzed by colorful and ubiquitous esterases. Large library of alcohols allow great variety of parcels to the prodrug(e.g., pKa and water solubility). slow rate asked long- chain aliphatic or sterically hindered alcohols faster rate asked EWG on the alcohol increased pKa or solubility choline- type or amino esters.

**Derivatization of amines:**

Owing to the slow in vivo fractionalization rate of the N- substituted amides, acylation of amines is generally not recommended. More possibilities are offered by actuated amides, peptides, imines and soft quaternary ammonium mariners. still, the use of simple N- acyl derivations mustn't totally be discarded. The N- benzoyl- or N- pivaloyl derivations of the inhibitory neurotransmitter GABA are exemplifications of composites suitable to access the blood – brain hedge.

**Derivatization of medicines containing a carbonyl function aldehydes and ketones exemplifications of carrier linked prodrug Prodrugs for Advanced immersion and Distribution**

Fluocinolone aceteonide and flucinonide are corticosteroid prodrugs that allow dermal immersion by “ masking ” the hydroxyl groups( that can interact with the skin or list spots in the keratin) as either esters or acetonides. Once absorbed through the skin, the true medicine is revealed by esterases or hydrolysis.

Dipivefrin is a prodrug for the antiglaucoma medicine epinephrine. The dipivaloyl esters allow for lesser corneal permeability which are hydrolyzed by corneal and waterless humor esterases. Prodrugs for Stability

Prodrugs may cover medicine from 1st- pass goods. Propranolol( antihypertensive medicine) suffers from first- pass elimination performing in dropped bioavailability of oral boluses compared to.v. injections. The hemisuccinate ester was designed to block glucuronide conformation performing in an 8-fold increase of tube situations of propranolol. Naltrexone( treatment for opioid dependence ) is nonaddicting and is readily absorbed from theG.I. tract and as a result undergoes expansive first- pass metabolism.

Prodrug for point specific medicine delivery Bodor & Associates developed a reversible redox medicine delivery system for getting medicines into the CNS. Exploitation of enzymes set up generally at the target point of action. For illustration, excrescence cells possess advanced attention of phosphatases and amidases than normal cells. Diethylstilbestrol diphosphate was designed for similar point-specific delivery of diethylstilbestrol in the treatment of bone cancer.

**Bioprecursors**

Bio Precursors results from the molecular revision of the active emulsion. There's no need of promoiety in bioprecursor prodrugs. The bioprecursor prodrugs are metabolized into a new emulsion that may be active or it may be farther metabolized to release the active emulsion. Reduction For illustration, Sulphapyridine a prodrug of Sulphasalazine.

**Macromolecule Prodrugs**

Spacer or Linker Prodrugs The spacer or linker approach can be used in the case where it's delicate to attach the promoiety with parent medicine directly due to steric interference or any other functional hedge. The spacers are adhered by enzymatic or chemical action on the bond between promoiety and spacer. For illustration, Fosphenytoin. The studies revealed that there are two main objects while designing and developing a prodrug that are Complete and fast conversion of the prodrug into its active medicine form. The below- said objects are interrelated to each other. The prodrug is developed to ameliorate the quality of the active medicine, its efficacy and its toxin. Thus, keeping in view the below points, a prodrug bracket system would be developed by Kuei- Meng Wu in 2009, on the basis of point of conversion into the active form of the medicine. According to this bracket prodrug is classified into two main classes

**Type I Prodrugs**

Type I class is further classified into two sorts Type IA and Type IB. Type IA is the prodrug that's metabolized at target cells. These include colorful antimicrobial and chemotherapeutic agents. Type IB is the prodrug which is metabolized in metabolic like liver and GI mucosal cells.

**Type II Prodrugs**

These are the prodrugs which are metabolized extracellularly. Further, Type II prodrugs are classified into three sorts, Type IIA, Type IIB and Type IIC. Type IIA is the prodrugs which are metabolized in GI fluid. Type IIB is metabolized in systemic rotation or other extracellular chambers. Type IIC are the prodrugs which are metabolized at target towel/ cells.

**Prodrugs with improved aqueous solubility**

Since the 1990s once with the appearance of combinational chemistry and high throughput screening methods the number Prodrug design may be useful in circumventing problems associated with Solubility immersion and distribution point non particularity Insecurity prolonged release toxin poor case adequacy (unwelcome taste or odor) expression problems. The purpose of prodrug conflation in utmost cases is increasing bioavailability. In medicine development there are some important physicochemical parcels such as applicable solubility, acceptable lipophilicity, good permeability, which are explosively told by acid- base parcels of the operativecules. Prodrugs with better lipophilicity In numerous specifics a carboxyl functional group exists as a necessary function for their pharmacological exertion. Still, its presence causes too high opposition for oral announcement- ministry, as in the small intestine at pH 5- 7 it's largely ionized, which prevents the passage of motes through membranes by unresistant prolixity. Esterification of these groups with short or long aliphatic alcohol is the most extensively habituated system. ACE impediments are substantially ethyl ester prodrugs( enalapril, trandolapril, quinapril, benazepril). Ethyl esters considerably increase lipophilicity, therefore adding immersion. Methyl ester occurs further infrequently, because by hydrolysis poisonous methyl alcohol is released. Thus this system of design of prodrugs is used only in case of low cure medicines, independently in the case of esters with veritably short duration of drug candidates with visible poor water solubility has increased. These compounds generally have high molecular weight, are lipophilic, their absorption being limited by inadequate solubility. It has been managed to solve this problem by using prodrug strategy.

Solubilization in water can be increased by the insertion of *polar structures*, thus enabling oral or parenteral administration.

The solubility adding polar groups can benonioniz- suitable groups but which are fluently demeaning in the body. A frequently presented illustration is the non-steroidal anti-inflammatory sulindac, which is the sulfoxide outgrowth of the active form. The active metabolite is formed by reduction of a more polar, more answerable prodrug. Another possibility is binding of the pharmacon to a hydrophilic polymer directly or by a linker; cut, 4. Metabolism of Sulindac 360 Kelemen Hajnal etal./ Acta Medica Marisiensis.

 examples of pro moieties for better waterless solubility polyglutamate acid, dextran, chitosan are most commonly used. Insertions of ionic groups similar as phosphate esters have lesser connection. The prodrugs of phosphate esters are profitable because, by forming mariners, they've a good solubility, are fleetly dissolved in gastro- intestinal tract and are hydrolyzed in the presence of alkaline phosphatase enzyme present on the mucosal face. An formerly activat- ed form diffuses into the cell (e.g. fluconazole, phenytoin). propofol( Aquavan) is the phosphoryl oxy methyl ether of propofol, it's slightly answerable in water, doesn't beget vexation at the injection point compared to propofol, the parent patch used as an o/ w conflation injection. carrying parenteral medications of sparingly answerable active substances can be fulfilled by esterification with dicarboxylic acids, this system being used for a long time. It's known that the sodium swab of chloramphenicol- gap hydrogen succinate is one hundred times further answerable than chloramphenicol itself, so it's suitable for the prepraportion of parenteral result. It should be observed that parenteral prodrugs may experience problems concerning-corresponding stability by forming precipitates; some prodrugs can not be heat castrated due to corruption. Targeted medicine delivery The efficacy criterion in certain remedy is point-specific medicine delivery, when organ/ towel specific medicines are administered and amended in the targeted organ. This is a great challenge for experimenters in the pharmaceutical assiduity, prodrug conflation playing an important part in this field. Grounded on exploration results we'd like to emphasize two directions of application of prodrugs: excrescence targeting and antigen navigator- geting. Prodrugs in cancer remedy The effectiveness of cancer chemotherapy would increase if the active substance would reach the targeted excrescence cell without damaging body cells.

Thus delivery to target spots with the help of prodrugs is a precedent in medicine exploration. Excrescence particularity may be achieved in numerous ways, similar as by use of enzymes or transporters, or the development of prodrug- antibody which is widely honored by excrescence cells. It's an advantage if the medication can be administered also orally. An illustration of success is capecitabine, a prodrug of 5- fluorouracil( 5- FU), that requires a waterfall of three enzymes for the bioconversion to the active medicine. The first declination takes place in the liver by carboxyl esterase, when pentyl alcohol, of lipophilic character, is excluded. This is followed by deamination by cytidine deaminase enzyme present in both the liver and excrescence cells, followed by picky release of 5- FU in the excrescence cells under the action of thymidine phosphorylase, which shows much advanced exertion in excrescence cells than in normal cells. The prodrug is absorbed fleetly and nearly fully from the gastrointestinal tract and provides high attention of 5- FU in targeted excrescence cells. Capecitabine is used orally in metastatic colon cancer and in combination remedy in other types of cancer. Prodrugs having better water solubility. The poor waterless solubility of the numerous active remedial agents is of major concern as these active agents retain implicit remedial exertion. In achieving optimum solubility is one of the topmost challenges in medicine discovery. The objectification of prodrug approach helped to overcome the problem of waterless solubility of numerous remedial agents by perfecting dissolution rate. This can be done by the application of esters and amides of amino acids and phosphoric acid. Among these phosphate esters are extensively used to enhance the waterless solubility of orally and parenterally administered medicines. Endogenous phosphatase enzymes release the active parent medicine from the phosphate ester prodrug ,e.g prednisolone sodium phosphate prodrug, phenytoin sodium. The amino acid esters and amide prodrugs are also used to ameliorate the waterless solubility of active parent medicines e.g valacyclovir and valganciclovir which are valine esters of the antiviral medicines acyclovir and ganciclovir. The waterless solubility of acyclovir is set up to be 15- 30, while its valine- prodrug exhibits 50 waterless solubility. These prodrugs are good substrates of small peptide transporters (PEPT 1) present in intestinal epithelial cells. Prodrugs with better lipophilicity The natural membranes correspond to phospholipids, thus, lipophilicity is needed to transport through natural membranes. The lipophilicity of polar and ionized medicines can be bettered by converting them into esters. The hydrophilic groups present in parent medicines like hydroxyl, thiol, carboxyl, phosphates and amines can be converted to further lipophilic aryl and alkyl esters. These esters can be converted to their active parent medicine by the enzymatic action of esterases. For illustration, Dabigatran, which is polar and permanently charged patch and thus has veritably low bioavailability due to high opposition. The bioavailability of dabigatran was enhanced by the preface of dabigatran prodrug which acts by masking the polar functionalities with carbamic acid ester and carboxylic acid ester groups. Another illustration includes o- butyryl timolol, a prodrug of timolol having logP/ D value of 2.08 while that of timolol logP/ D is-0.04. Chemotherapeutic prodrugs for bettered targetability and efficacity Chemotherapy is used to treat numerous diseases. One of the main complaints treated by chemotherapeutic agents is cancer. The maturity of anticancer agents exerts their on costatic action by inhibition of proliferation and arresting cell cycle at a certain stage. But these on costatic medicines have poor selectivity in opting excrescence cells, so they affect not only excrescence cells but also normal cells. Thus, this problem decreases the effectiveness of these agents for long- term use. This problem is overcome by the prodrug approach. An anticancer prodrug should be transported to neoplastic cells and there it'll go through a conversion to cytotoxic parent medicine by original or recombinant enzymes. Anticancer medicines can be intended to target specific notes that are largely expressed in excrescence cells as compared to normal cells. The new chemotherapeutic prodrugs include Enzyme- actuated prodrug remedy, which is further divided into Antibody- directed enzyme prodrug remedy( ADEPT) and Gene- directed enzyme prodrug remedy( GDEPT), Target ligand conjugated prodrugs, enzyme- cleavable prodrugs, membrane transporter associated prodrugs and polymeric prodrugs. Effect of prodrugs on Pre-systemic metabolism and excretion The vacuity of the medicine in systemic rotation is affected by pre-systemic metabolism in the gastrointestinal tract and in liver. This pre-systemic metabolism results in the presence of a shy volume of medicine at the point of action or target. This problem has been overcome by colorful styles of altering the route of administration and by expression development eg sublingual route and by controlled release phrasings. Pre-systemic metabolism can also be inhibited by the prodrug approach by masking the metabolically labile functional groups, e.g terbutaline undergoes rapid-fire pre-systemic metabolism, thus, it has been averted by converting its phenolic groups to bis-dimethyl carbamate. Another problem of expansive excretion is associated with a more waterless solubility of the parent medicine. This can be controlled by incorporating lipophilic properties. The part of prodrugs for CNS delivery The development of medicines acting on CNS faces one major problem that's the incapability of numerous remedial composites to cross the blood- brain hedge( BBB). The composition of BBB involves the endothelial cells of brain micro-vessels connected by veritably tight junctions. thus, the passage of the composites through BBB can be achieved by the aid of a carrier involving natural transporter proteins localized on the luminal and abluminal sides of epithelial cells. So there are principally three mechanisms for a emulsion to enter the brain. adding the unresistant prolixity by masking polar groups. adding the carrier- intermediated or receptor- intermediated transport through BBB. dwindling the efflux of medicine from the brain into the blood. The colorful endogenous transporters present at the brain capillary endothelial which forms BBB are LAT1( Large neutral amino acid transporters) MCT( Monocarboxylic acid transporters) GLUT1( Glucose transporters) PEPT1( Peptide transporters) OCT( Organic cation transporters) OAT( Organic anion transporters Prodrugs as substrates The medicine has to bypass colorful pharmacokinetic and pharmaceutical walls after administration. To overcome this problem, currently a point- picky medicine delivery approach is use die prodrug design approach. The prodrugs act as substrates for colorful endogenous natural transporterses. Gabapentin enacarbil is a prodrug of gabapentin which is substrate for monocarboxylic acid transporter- 1

(MCT) and Sodium-dependent multivitamin transporter (SMVT) located each over the intestine. Gabapentin enacarbil is having better immersion, bioavailability, and pharmacokinetic parcels than parent medicine gabapentin. Other exemplifications are ACE impediments, antiviral medicines, and anticancer prodrugs act as a substrate for( Pept-1)

# The role of prodrugs for CNS delivery:

The development of drugs acting on CNS faces one major problem that is the inability of many therapeutic compounds to cross the blood-brain barrier (BBB). The composition of (BBB) involves the endothelial cells of brain micro-vessels connected by very tight junctions. Therefore, the passage of the compounds through BBB can be achieved by the aid of carrier involving intrinsic transporter proteins localized on the luminal and abluminal sides of epithelial cells. [21] So there are basically three mechanisms for a compound to enter the brain.

* 1. Increasing the passive diffusion by masking polar groups.
	2. Increasing the carrier-mediated or receptor-mediated transport through BBB.
	3. Decreasing the efflux of drug from the brain into the blood.

The various endogenous transporters present at the brain capillary endothelial which forms BBB are:

LAT1 (Large neutral amino acid transporters) MCT (Monocarboxylic acid transporters) GLUT1 (Glucose transporters**)**

PEPT1 (Peptide transporters)

OCT (Organic cation transporters) OAT ( Organic anion transporters)

CNT ( Concentrative nucleoside and nucleotide transporters)

To improve the bioavailability and permeation of drug through BBB, the targeted prodrug approach has been suggested as a potential alternative. The targeted prodrugs synthesis depends on the types of cells and tissues, types of enzymes and transporters present at the target site. In- depth knowledge about transporters, enzymes at the target site and their interaction with parent drug or ligand to get them recognized at the target site are required before synthesis of the prodrug. [23, 24] For example, Thiorphan has limited BBB permeability but thiol derivatives of thiorphan have been proven with remarkable BBB permeation and therefore high analgesic effect. These derivatives are the mono-acylated product of thiorphan (S-acetyl thiorphan, 18) and benzyl ester of S-acetyl thiorphan (Acetorphan).

**Approaches to Prodrug Design For Desired Distribution At Target Site**

Prodrugs can be designed to target specific carriers or enzymes to overcome the undesirable properties of the parent drug. This type of targeted prodrug design requires a thorough knowledge of carrier systems and enzymes which can be used in targeting. Therefore, the two main categories in which the targeted prodrugs will be divided are Targeting specific membrane transporters and Targeting specific enzymes.

#  Prodrug Design Targeting Membrane Transporters

There are numerous therapeutic agents which have achieved a remarkable improvement in their absorption across the biological membranes with the help of transporters. These transporters play a vital role in absorption, distribution, and elimination of drugs. It is therefore very important to study the nature and functions of these transporters as they have a major role in altering the pharmacokinetic properties of the drug. It has been suggested that a given drug will interact with these membrane transporters during disposition in the body. The transporters are widely distributed in the body especially in the organs like intestine, liver, and kidney as these organs play a remarkable role in absorption, distribution and elimination processes. The drug transporters are widely categorized into two groups i.e SLC (Solute carriers) and ABC (ATP- binding cassette). The transporters move the substrate in either direction across the cell membrane so depending on the direction of movement these can be classified as efflux transporters and influx transporters. The ABC transporters are efflux transporters because they utilize the energy from the hydrolysis of ATP for the active export of substrate from intracellular to the extracellular milieu. The SLC transporters are influx transporters because they make possible the cellular uptake or influx of substrate by facilitated diffusion. There are few SLC transporters which act as both efflux and influx transporters or bidirectional depending on the concentration gradient of the substrate and the ions coupled across the membrane. At this point, it is important to understand the interplay between the transporters present in the apical and basolateral membranes of epithelial cells. This study of efflux and influx transporters is mandatory to determine the degree and direction of drug movements in the organs like intestine, liver, and kidney. The transporters located in intestine, liver and kidney .

**Application of Prodrugs**

Several drug candidates fail to pass clinical trial phase due to their poor pharmacokinetic profiles such as low aqueous solubility, poor membrane permeability, chemical instability, toxicity etc. Hence, understanding the pharmacokinetic properties of the lead molecules at an early discovery phase and the prodrug strategy is one of the most popularly practised approach to overcome the pharmacokinetic barriers. A number of success stories of prodrugs in the recent years is surely a stimulating factor for the scientific community to utilize this approach. Most of the reported prodrugs have been synthesized based on the chemists’ knowledge andexpertise. However, in this current era of targeted drug discovery, there is an emerging preference and need for a data driven computational modelling before going for any wet lab synthesis, to design more efficacious and selective prodrugs. So, one must have an abstract understanding of the pharmacokinetic properties and their relation with the chemical structures and functional groups of the parent drugs in order to design a suitable prodrug. In this scenario, the reported *in vitro* and *in vivo* data along with the *in silico* predictive modelling would be very useful to achieve the pre-design understanding. Prodrug provides the users with such experimental data curated from the literature and also several predicted properties of the existing prodrugs as well as their active drugs. It enables the user to visually compare the structures of the known prodrugs and their active compound and relate the structural differences with the improvements in the pharmacokinetic properties with the help of quantitative/qualitative experimental data provided therein. The user can easily make datasets relevant to their molecules of interest and can quickly design a QSAR study to predict new prodrugs. This Bottom‑up approach can support the decision-making process and distinguish prodrug candidates with a greater chance of success. Furthermore, through the browse options one can obtain a list of prodrugs reported for a certain disease, drug target or a list of prodrugs activated through a certain group of enzymes or a certain mechanism. This will be helpful to accelerate the design of targeted prodrugs or rational prodrugs. Prodrug integrates all type of data (experimental ADMET properties, physicochemical properties, predicted pharmacokinetic properties, structural properties, data on enzymes, targets, diseases etc., in a sigle platform to give a holistic view of the profiles of the prodrug and the active. Thus we believe that Prodrug with its detailed literature curated experimental, predicted and structural data on the existing small molecule prodrugs, will facilitate the scientific community for targeted prodrug approaches

# The impact of the prodrug strategy on current treatments & what the future holds:

The anti-HCV agent Sofosbuvir is a recent example of the huge success of a prodrug. As mentioned above, nucleoside analogues exhibit great potential in the therapy of viral infections and cancer by interfering with the replication machinery. A critical parameter for the activity of a nucleoside analogue is the kinetics of its phosphorylation, ultimately yielding the triphosphate as the active compound - that is the nucleoside analogue itself being a prodrug. Often, however, the first, highly specific phosphorylation step is low in rate. Moreover, the dependency of the nucleoside analogue being activated by kinases can lead to resistances. Since nucleotides are unable to passively penetrate cell membranes due to their high charge and are rapidly dephosphorylated while circulating, prodrug systems masking the phosphate group have been developed. Sofosbuvir is an amidate prodrug (based on the Pro-Tide-concept developed by McGuigan) of the monophosphate of a 2’- deoxy-2’-fluoro-2’methyl uridine analogue. The negative charges of the phosphate group are masked by 1) esterification with phenol and 2) the amidate group consisting of an amino acid ester. The nucleotide is set free by firstly the action of cellular carboxyl esterases. The cleavage of the amino acid carboxyl ester then initiates a cyclization, displacing the phenol. After hydrolysis of the intermediate a second enzymatic reaction yields the nucleotide, which is then further phosphorylated.

When orally administered, the prodrug is directly gated from the GIT to the liver by the portal vein. Since in the hepatocytes the concentration of carboxyl esterases is quite high, the first step of the nucleotide- delivering metabolism of the prodrug immediately appears in these cells. This is why Sofosbuvir is not only a nucleotide prodrug that facilitates the diffusion of the monophosphate through the cell membrane but also targets the drug to hepatocytes, the very cells infected with HCV. The FDA approved Sofosbuvir in 2013. It shows a high cure rate: clinical studies indicated that in up to 90% of chronically infected patients, the virus was no longer detectable after treatment in combination with conventional therapeutics. This is unprecedented in the treatment of chronic Hepatitis C.

In the case of some nucleoside analogues the first phosphorylation is not the only limited step. Meier and coworkers recently introduced a concept for bio-reversibly masking the charges of nucleoside analogue di- and even triphosphates. The bypass of all three phosphorylating steps of nucleoside analogues might have great impact on future antiviral and anticancer medication. By this means, nucleoside analogues, which had been ‘dropped’ before, could now unfold their therapeutic potential that was hampered by failure of phosphorylation.By virtue of this, new agents will likely become available for the treatment against viral infections and malignant neoplastic diseases that pose major threats to society.

It should also be noted that antibiotic resistance has become the major worldwide health issue. Many efforts are currently underway to generate new antibacterial compounds. Here, prodrug strategies must be considered to include promising drug candidates, which show e.g. low metabolic stability or solubility as in Tedizolid phosphate, the phosphate prodrug of the antimicrobial agent Tedizolid, which shows activity against methicillin-resistant Staphylococcus aureus.

#  Prodrug Design: Targeting Specific Enzymes

The enzyme-targeted prodrug design approach can be widely used to improve oral absorption of drugs and also site-specific drug delivery. Enzymes can be an important target for improving oral drug absorption of the drugs. Secondly, approach is site-specificity which is a very important aspect for precise and direct effects at the site of action with minimal effect on rest of the body.

**Enzyme-Targeted Prodrug Approach for Site-Specificity:** The enzyme-targeted site-specificity nowadays has been suggested to play a vital role in chemotherapy of cancer. This has been found that high concentrations of activating enzymes provide site-specificity to the prodrugs and responsible for the effective treatment of animal tumors. It was found that human tumors containing high concentrations of activating enzymes were rare So, it was a major problem of using the enzyme- targeted approach in the treatment of human tumors. It has been suggested that this problem is resolved with the introduction of newer techniques which helps in the localization of prodrug activation enzymes in the specific tumor cells prior to the administration of prodrug. These techniques are referred as:

ADEPT (Antibody Directed Enzyme Prodrug Therapy) GDEPT (Gene Directed Enzyme Prodrug Therapy).

#  General Concept of ADEPT and GDEPT for Site-Specificity of Prodrugs

In ADEPT strategy, the drug-activating enzyme is localized onto the tumor cell surface by forming conjugate with a monoclonal antibody which targets only tumor cells. The non-toxic prodrug is administered systemically which is converted to a toxic drug by the pre-localized drug-activating enzyme resulting is cytotoxic effects in tumor cells. It has been shown that

various classes of human tumor xenografts are sensitive to ADEPT by using combinations of different antibodies, enzymes, and prodrug. In GDEPT strategy, it consists of a prodrug which is an inactive form of the active drug which is delivered to the body systemically and a gene which is decoded at target cells to form the enzyme. The vectors are used to transport prodrug activated enzyme gene to tumor cells and normal cells. The main challenge in GDEPT is vector delivery. It has been suggested that there are main two types of strategies i.e 1) Search & destroy approach and 2) Induction approach.

In search & destroy strategy, vector identifies the tumor cells selectively and kill the tumor cells whereas in induction strategy vector is delivered locally to stimulate the immune system and therefore killing the tumor cells. The selection of vectors for the delivery of gene is a very crucial step in terms of efficacy in this strategy. The vectors may be synthetic in origin or more commonly used that are derived from microbes like viruses and bacteria. The second major concern in both ADEPT and GDEPT is the selection of enzyme. The general considerations while selecting enzyme for ADEPT and GDEPT are as follows:

1. The enzyme would be monomeric and of low molecular weight so that it would be easy to handle and protein modification would be possible.
2. The enzymes from the non-human or non-mammalian origin are preferred targets.
3. The enzymes from the microbiological origin are of significant importance in terms of specificity.

**Barrier of prodrug and overcome techniques**

Prodrugs can offer several advantages in drug development and therapy; however, they also come with certain challenges. Some common barriers associated with prodrugs and the techniques used to overcome them include: Metabolic Activation: One of the primary challenges in prodrug design is ensuring reliable and efficient activation of the prodrug to its active form in the body. To overcome this barrier, researchers carefully choose specific chemical modifications that facilitate the prodrug's metabolism through enzymatic or non-enzymatic pathways. Enzyme-responsive prodrugs, prodrugs activated by pH changes, or prodrugs that are susceptible to specific metabolic enzymes are some techniques used to achieve controlled activation. Stability: Prodrugs must remain stable during storage and transit until they reach the intended site of action. Chemical modifications are employed to enhance the prodrug's stability, preventing premature activation or degradation. Nanoparticle-based delivery systems and protective coatings are other techniques used to improve prodrug stability. Specificity: Achieving site-specific drug release and targeting is crucial to minimize off-target effects and enhance therapeutic efficacy. Various strategies are employed, such as using prodrugs that are selectively activated by enzymes present only at the target site or designing prodrugs that are preferentially taken up by specific cells or tissues. Toxicity: Prodrugs may carry inherent toxicities due to the chemical modifications themselves or potential toxic by-products upon activation. Extensive preclinical testing and structure-activity relationship studies are conducted to ensure that prodrugs do not introduce additional toxicities. Additionally, targeted delivery and controlled release can help minimize exposure to healthy tissues, reducing the risk of adverse effects. Bioavailability: Some prodrugs may have poor bioavailability, making it challenging to achieve effective drug concentrations in the bloodstream or the target site. Techniques to improve bioavailability include using prodrugs with enhanced solubility, formulation into liposomes or nanoparticles, or incorporating permeation enhancers. Patient Compliance: Prodrugs can be designed to enhance patient compliance by reducing the frequency of dosing or improving the overall patient experience, such as using tasteless or less irritating prodrug formulations. Pharmacokinetics: Designing prodrugs with favorable pharmacokinetic properties is crucial for achieving desired drug concentrations and duration of action. For example, prodrugs may be engineered to have prolonged half-lives or to bypass efflux transporters that can limit drug absorption. Drug Resistance: Some diseases may develop resistance to certain drugs, including prodrugs. To overcome this, researchers may explore combination prodrug therapies or use different activation pathways to regain drug effectiveness. Patent Protection: Prodrugs may present challenges related to patent protection since the modifications made to the active drug can affect patent eligibility. Pharmaceutical companies often need to carefully consider patent strategies to protect their prodrug innovations. Overall, prodrugs offer an inventive approach to drug development, and researchers continually explore innovative techniques to overcome the barriers associated with their design, activation, and therapeutic benefits. The success of prodrugs relies on a deep understanding of drug metabolism, pharmacokinetics, and disease biology, along with rigorous preclinical and clinical evaluation.

**Major Chemical Moieties For Prodrug Design**

As per the information about prodrug design, molecular modification in the parent drug is the main strategy adopted to alter the physicochemical and pharmacological profile of the parent drug. There are many functional groups which act as carriers are available for molecular modification but their choice depends on the chemical groups or moieties already present on parent drug. These chemical groups or carriers which can be incorporated in the structure of parent drug are mainly Esters, Amides, Carbamates, Phosphates.[70] In this section of the article, we will discuss them one by one in details*.*

**(i) Prodrugs with Esters:** Esters are the promising bond linking groups due to their capability of undergoing hydrolysis easily. From the literature search, it has been found that there are many examples of esters prodrugs which have attained more aqueous solubility than the parent drug. For example, palmarumycin, etoposide, NSAIDS and many antiviral drugs. We will hereby discuss few examples to understand the intensity of the effect of prodrug design on aqueous solubility of the parent drug.

1. Palmarumycinis a lipophilic drug with poor aqueous solubility, therefore it was suggested that this drug has shown poor anticancer activity *in vivo*. So, the chemists synthesized the amino-ester prodrugs of palmarumycin. They designed glycyl esterderivative which was found to be about seven times increased aqueous solubility than the parent drug.

Etoposide which is a topoisomerase inhibitor having low aqueous solubility. The prodrug design was adopted and prodrugs were synthesized whose aqueous solubility was demonstrated as about 120 folds higher than the parent drug. The prodrug of etoposide shown belowattains water solubility of about 9.0 mg/ml as compared to etoposide which has 0.1 mg/ml of water solubility.

#

1. Diclofenac esterprodrugs of Diclofenacwere synthesized by chemists and it was found that glycerol ester has been shown better water solubility of about 0.551 µmol/ml as compared to parent drug having 0.0034 µmol/mL of water solubility.

**(b) Prodrugs with Amides:** The amide prodrugs are also promising compounds for increasing aqueous solubility of parent drug and its bioavailability. As compared to esters, amide bonds are more stable to enzymatic hydrolysis. There are numerous examples of amide prodrugs, some are discussed below:

**(a)** DW2282is chemically (S)-1-[1-(4-aminobenzoyl)-2,3-dihydro-1H-indol-6-sulphonyl]- 4-phenyl-imidazolidin-2-one, which is an anticancer drug with low water solubility (0.024 mg/mL) and higher gastrointestinal toxic effects. Many amino acid prodrugs were synthesized almost all of them attained higher water solubility as compared to the parent drug. One of the compound have shown very good aqueous solubility (0.865 mg/mL) and bioavailability by oral route

Acyclovir is another example with poor aqueous solubility. It is an antiviral drug having a low bioavailability of about 10% to 20 %. To overcome these problems of low bioavailability and poor aqueous solubility, an amide prodrug and ester prodrug were synthesized. Both the prodrugs showed a remarkable increase in water solubility i.e amide prodrug showed about 17-fold higher aqueous solubility than parent drug and ester prodrug showed about 9-fold higher water solubility than the parent drug.

**(c) Prodrugs with Phosphates:** The phosphate prodrugs have been proven good candidates to increase the aqueous solubility and bioavailability of the parent drug. The phosphate prodrugs get converted to its parent drug by the action of intestinal alkaline phosphatase enzyme.

1. Flores-ramos *et al.* synthesized a prodrug of benzimidazole derivative i.e α-6-chloro-2- (methylthio)-5-(napthalen-1-yloxy)-1H-benzo[*d*] imidazole. The prodrug synthesized by linking disodium phosphate to the structure and found be 50,000-folds higher water soluble than the parent drug.
2. Another lipophilic drug which encounters difficulty in aqueous solubility is propofol. The phosphate prodrugs were synthesized to overcome this problem either by directly attaching phosphate group to hydroxyl group of parent drug or by using spacers such as oxymethyl and ethylenedioxy moieties.

**(d) Prodrugs with Carbamates:** Carbamates are derivatives of carbamic acid. The carbamates are generally exhibited very good chemical and proteolytic stability. Carbamates are able to permeate through cell membranes and also they have the capability to alter intermolecular and intramolecular interactions with the target receptor or enzyme. Due to their contribution in drug designing carbamates have received special attention since past few years.

**(a)** Histone deacetylases are responsible for gene expression and several inhibitors of histone deacetylases exhibit anti-tumor activity. One of the histone deacetylases inhibitor is a benzamide compound CI-994 **.**The poor aqueous solubility of this compound limits its therapeutic activity. To overcome this problem, Thomas M. *et al* have synthesized two glucuronide prodrugs. In one compound they have linked glucuronide moiety with the aid of spacer and in another compound they have directly linked the glucuronide moiety with the carbamate groupof parent drug. The aqueous solubility of parent compound CI-994 was found to be 0.08 mg/mL and both the prodrugs showed aqueous solubility more than 1 mg/mL.

**Significance of prodrug design**

Prodrugs are chemically modified versions of active pharmaceutical compounds that are designed to undergo specific metabolic changes in the body to convert them into their active form. The significance of prodrugs lies in their ability to enhance the pharmacokinetics, pharmacodynamics, and overall therapeutic effectiveness of certain drugs. Here are some key reasons why prodrugs are used: Improved bioavailability: Prodrugs can be engineered to improve drug solubility, stability, and absorption. By modifying the chemical structure of the active drug, prodrugs can overcome barriers that might otherwise hinder its efficient delivery and uptake in the body. Reduced side effects: In some cases, the active form of a drug might cause unwanted side effects or toxicities. Prodrugs can be designed to reduce or avoid these adverse effects by controlling the rate of drug release or targeting specific tissues. Prolonged duration of action: Prodrugs can be formulated to release the active drug slowly over an extended period, leading to a prolonged therapeutic effect. This can reduce the frequency of dosing and improve patient compliance. Enhanced target specificity: Prodrugs can be engineered to be selectively activated at the target site or by specific enzymes, enhancing the drug's effectiveness while reducing off-target effects. Overcoming drug resistance: Some prodrugs can bypass drug resistance mechanisms that may develop in certain diseases. By using alternative activation pathways, prodrugs can regain their therapeutic effectiveness in resistant cases. Masking of bitterness or unpleasant taste: Certain drugs have a bitter or unpleasant taste, which can affect patient adherence to treatment. Prodrugs can be designed to be tasteless or have a more acceptable taste, making them easier for patients to take. Facilitating administration routes: Prodrugs can be tailored to suit specific routes of administration, such as oral, intravenous, or topical. This flexibility in formulation allows for a more convenient and efficient drug delivery system.Patent protection: Developing a prodrug of an existing active compound can extend patent protection and provide pharmaceutical companies with additional exclusivity and market opportunities. Despite these advantages, prodrugs also come with their challenges, such as the need for precise metabolic activation and potential issues related to toxicity or unforeseen side effects from the prodrug itself. Careful consideration and extensive testing are required during the development of prodrugs to ensure their safety and efficacy before they can be approved for clinical use.

**Example of prodrug**

Here are some more examples of prodrugs: Clopidogrel (Prodrug of Clopidogrel active metabolite): Clopidogrel is an antiplatelet medication used to prevent blood clots in conditions like acute coronary syndrome and after stent placement. It is administered orally and undergoes hepatic metabolism to produce its active metabolite. The active metabolite inhibits platelet activation and aggregation, reducing the risk of clot formation. Oseltamivir (Prodrug of Oseltamivir carboxylate): Oseltamivir, commonly known as Tamiflu, is an antiviral medication used to treat influenza (flu) infections. Oseltamivir is a prodrug that is converted to its active form, Oseltamivir carboxylate, in the liver. Oseltamivir carboxylate inhibits the neuraminidase enzyme of the influenza virus, reducing viral replication and easing flu symptoms. Enzyme Replacement Therapies (ERTs): Some enzyme replacement therapies used to treat genetic disorders, such as Gaucher's disease, Fabry disease, and Pompe disease, utilize prodrug forms of the deficient enzyme. The prodrug is engineered to be taken up by cells and then converted into the active enzyme, compensating for the missing or dysfunctional enzyme in patients. Codeine (Prodrug of Morphine): Codeine is an opioid analgesic commonly used for pain relief and cough suppression. It is metabolized in the liver into its active form, morphine. The conversion to morphine is responsible for codeine's analgesic effects. Prednisone (Prodrug of Prednisolone): Prednisone is a corticosteroid used to treat various inflammatory conditions and immune-related diseases. After oral administration, it undergoes hepatic conversion to prednisolone, its active form, which exerts anti-inflammatory and immunosuppressive effects. Azathioprine (Prodrug of Mercaptopurine): Azathioprine is an immunosuppressive drug used to prevent organ rejection in transplant patients and to treat autoimmune diseases. It is converted into mercaptopurine, its active metabolite, which interferes with DNA and RNA synthesis, thereby suppressing the immune response. Valganciclovir (Prodrug of Ganciclovir): Valganciclovir is an antiviral prodrug used to treat cytomegalovirus (CMV) infections, especially in immunocompromised patients. Once inside the body, it is rapidly converted into its active form, ganciclovir, which inhibits viral DNA synthesis and replication. These examples highlight the versatility of prodrugs in various therapeutic areas, including antiviral, anticoagulant, anti-inflammatory, and enzyme replacement therapies. Prodrugs play a crucial role in improving drug efficacy, reducing side effects, and enhancing patient compliance, making them an important aspect of modern pharmaceutical development.

**Recent search on prodrug**

Prodrugs continue to be an active area of research and development in the pharmaceutical industry. Researchers are constantly exploring new prodrug strategies to improve drug delivery, enhance therapeutic efficacy, and reduce side effects of existing medications. Some recent trends and advancements in prodrug research include: Targeted Delivery: Scientists are developing prodrugs that can be activated selectively at the site of action. These targeted prodrugs aim to improve drug specificity, reduce off-target effects, and increase therapeutic outcomes. Enzyme-Responsive Prodrugs: Prodrugs that are specifically designed to be activated by certain enzymes present at the target site are gaining attention. This approach allows for precise drug release and activation in specific tissues or cells, potentially leading to enhanced treatment efficacy. Prodrugs for Gene Therapy: Prodrugs are being explored as delivery vehicles for gene therapy. By attaching therapeutic genes to prodrugs, researchers aim to achieve more efficient and controlled gene delivery, reducing immune responses and improving the safety of genetherapies. Nanoparticle-Based Prodrugs: Integration of prodrugs into nanoparticles is being investigated as a means to improve drug stability, solubility, and targeting capabilities. Nanoparticles can enhance drug delivery to specific tissues or cells, making them promising carriers for prodrug-based therapies. Personalized Medicine: With the advancement of genomics and precision medicine, researchers are exploring prodrug strategies that can be tailored to individual patients' genetic profiles, leading to personalized treatment approaches with optimized drug responses and minimized side effects. Combination Prodrug Therapies: Scientists are investigating the use of combination prodrug therapies, where multiple drugs are linked together in prodrug form. This approach can improve drug synergism, reduce resistance, and enhance therapeutic outcomes in certain diseases. Research in prodrugs is an exciting field with the potential to revolutionize drug development and patient care. As new discoveries emerge, prodrugs are likely to play an increasingly important role in optimizing drug therapies and addressing medical challenges. For the most recent updates and specific research papers on prodrugs, it's best to refer to academic journals, scientific publications, and reputable research databases.

**CONCLUSION**

In conclusion, prodrugs play a significant role in drug development and optimization of bioavailability, especially when considering their aqueous solubility and lipid solubility characteristics. Prodrugs are chemically modified versions of active pharmaceutical compounds designed to enhance their pharmacokinetic and pharmacodynamic properties, ultimately improving their therapeutic efficacy and patient compliance. Aqueous Solubility: Many drugs with poor aqueous solubility face challenges in effective absorption and distribution within the body. Prodrugs can be designed to improve the aqueous solubility of such drugs, making them more readily dissolved in bodily fluids and facilitating their absorption from the gastrointestinal tract. By increasing solubility, prodrugs can enhance bioavailability and overall drug performance. Lipid Solubility: The ability of drugs to pass through cell membranes and reach their target sites is influenced by lipid solubility. Prodrugs can be engineered to increase lipid solubility, enabling better penetration into cellular structures and improving drug uptake by tissues. This is particularly important for drugs that need to cross the blood-brain barrier or penetrate lipid-rich biological barriers. Drug Development Optimization: Prodrugs are often used to address limitations associated with the parent drug, such as poor solubility, stability, or unwanted side effects. By converting the active drug into a prodrug with improved properties, drug developers can optimize its therapeutic profile and extend its applications. Bioavailability: Prodrugs can significantly impact the bioavailability of a drug by enhancing its absorption, distribution, metabolism, and excretion (ADME) properties. Prodrug design can be tailored to improve oral bioavailability, reduce hepatic first-pass metabolism, or increase tissue targeting, ultimately leading to better drug concentrations at the desired site of action. Patient Compliance: Prodrugs can contribute to improved patient compliance by reducing dosing frequency or minimizing side effects. For instance, prodrugs with extended release properties can allow less frequent dosing, which can positively influence patient adherence to the treatment regimen.

The solubility characteristics of prodrugs are crucial in formulating suitable drug delivery systems. Prodrugs with enhanced solubility can be incorporated into various formulations, including solid dosage forms, nanoparticles, or lipid-based formulations, which can impact drug release profiles and overall therapeutic performance. In summary, prodrugs offer a versatile approach to drug development, enabling pharmaceutical scientists to address challenges related to aqueous solubility, lipid solubility, and bioavailability. Through innovative prodrug design and optimization, researchers can enhance drug properties, improve therapeutic outcomes, and ultimately provide more effective and patient-friendly treatments for a wide range of medical conditions.

**REFERENCES**

[1] K M Huttunen, H. Raunio, J.Rautio. Prodrugs from serendipity to rational design. Pharmacol Rev. 2011; 63:

750-771.

[2] V.J Stella. Prodrugs: some thoughts and current issues. J Pharm Sci. 2010;99: 4755-4765.

[3] B. Testa. Prodrugs bridging pharmacodynamic/pharmacokinetic gaps. Curr Opin Chem Biol. 2009;13: 338-344.

[4] J. Rautio, H. Kumpulainen, T. Heimbach, R. Oliyai, D. Oh, T. Jarvinen, J. Savolainen. Prodrugs: Design and

clinical applications. Nat Rev Drug Discov.2008; 7: 255-270.

[5] J.B Zawilska, J. Wojcieszak, A.B Olejniczak. Prodrugs: A challenge for the drug development. Pharmacological

Reports. 2013; 65: 1-14.

[6] A. Abu-Jaish, S. Jumma, R. Karaman. Prodrugs Overview in prodrug design- A new era. Nova, USA; 2014.

[7] S. Papot, I. Tranoy, F. Tillequin, J.C Floren, J.P Gesson. Design of selectivity activated anticancer prodrugs:

elimination and cyclization strategies.Curr. Med. Chem. Anticancer agents. 2002; 22: 155-185.

[8] Kuei-Meng Wu. A new classification of prodrugs: Regulatory Perspectives. Pharmaceuticals. 2009; 2: 77-81.

[9] P. Fasinu, V. Pillay, V.M Ndesendo, L.C du Toit, Y.E Choonara. Diverse approaches for enhancement of oral

drug bioavailability. Biopharm Drug Dispos. 2011; 32: 185-209.

[10] C.E Miller. Prodrug administration for enhancing the bioavailability of drugs with low molecular solubility.

Chem Biodivers. 2009; 6: 2071-2083.

[11] V.J Stella, K.W Nti-Addae. Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev. 2007;

59: 677-694.

[12] D. Vytla, R.E Combs-Bachmann, A.M Hussey, S.T McCarron, D.S McCarthy, J.J Chambers. Prodrug

approaches to reduce hyperexcitation in the CNS. Adv Drug Deliv Rev. 2012; 64: 666-685.

[13] G.E Granero, G.L Amidon. Stability of valacyclovir: implications for its oral bioavailability Int J Pharm. 2006;

317: 14-18.

[14] S. Jana, S. Mandlekar, P. Marathe. Prodrug design to improve pharmacokinetics and drug delivery properties:

Challenge to the discovery scientists. Current Med Chem. 2010; 17: 3874-3908.

[15] B.M Liederer, R.T Borchardt. Enzymes involved in the bioconversion of ester-based prodrugs. J Pharm Sci.

2006; 95: 1177-1195.

[16] W.G Eisert, N. Hauel, J. Stangier, W, Wienen, A. Clemens, J. Van Ryn. Dabigatran: an oral novel potent

reversible nonpeptide inhibitor of thrombin. Arterioscler Thromb Vasc Biol. 2010; 30: 1885-1889.

[17] S. Blech, T. Ebner, E. Ludwig-Schwellinger, J. Stangier, W. Roth. The metabolism and disposition of the oral

direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos. 2008; 36: 368-399.

[18] K.M Huttunen, J. Rautio. Prodrugs an efficient way to breach delivery and targeting barriers. Current topics in

Medicinal Chem. 2011; 11: 2265-2287.

[19] R. Mahato, W. Tai, K. Cheng. Prodrugs for improving tumor targetability and efficiency. Adv Drug Deliv Rev.

2011; 63:659-670.

[20] L.A Svensson, A, Tunek. The design and bioactivation of presystemically stable prodrugs. Drug Metab Rev.

1988; 19: 165-194.

[21] N.J Abbott, A.A Patabendige, D.E Dolman, S.R Yusof, D.J Begley. Structure and function of blood- brain

barrier. Neurobiol Dis. 2010; 37:13-25.

[22] M.M Patel, B.R Goyal, S.V Bhadada, J.S Bhatt, A.F Amin. Getting into the brain: approaches to enhance brain

drug delivery. CNS Drugs. 2009; 23:35-58.

[23] A. Dahan, M. Khamis, R. Agbaria, R. Karaman. Targeted Prodrugs in oral drug delivery:the modern molecular

biopharmaceutical approach. Expert Opin Drug Deliv. 2012; 9: 1001-1013.

[24] R. Karaman. Prodrugs design based on inter and intramolecular processes. Chem Biol Drug Des. 2013; 82: 643-

668.

[25] J.M Lacomte, J. Costentin, A. Vlaiculescu, P. Chaillet, H. Marcais-Collado, C. Llorens-Cortes, M. Leboyer, J.C

Schwartz. Pharmacological properties of acetorphan, a parentrally active “enkephalinase” inhibitor. J Pharmacol

Exp Ther. 1986; 237: 937-944.

[26] S.M Lambert, F. Mergen, J H Poupaert, P. Dumont. Analgesic Potency of S-Acetylthiorphan after intravenous

administration to mice. Eur J Pharmacol. 1993; 243: 129-134.

[27] P.D Dobson, D.B Kell. Carrier mediated cellular uptake of pharmaceutical drugs: an exception or the rule? Nat

Rev Drug Discov. 2008; 7: 205-220.

[28] T.M Sissung, S.M Troutman, T.J Campbell, H.M Pressler, H. Sung, S.E Bates, W.D Figg. Transporter

Pharmacogenetics: Transporter polymorphisms affect normal physiology, diseases, and pharmacotherapy. Discovery

Medicine. 2012; 13: 19-34.

[29] M. Brandsch, I. Knutter, E. Bosse-Doenecke. Pharmaceutical and Pharmacological importance of peptide

transporters. J Pharm Pharmacol. 2008; 60: 543-585.

[30] M.A Kamal, R,F Keep, D.E Smith. Role and relevance of PEPT1 in drug disposition, dynamics and toxicity.

Drug Metab Pharmacokinet. 2008; 23:236-242.

[31] W.J Jonker, A.H Schinkel. Pharmacological and physiological functions of the polyspecific organic cation

transporters: OCT1,2 and 3 (SLC 22A1-3). J Pharmacol Exp Ther. 2004;308: 2-9.

[32] W.M Suhre, S. Ekins. C.Chang, P.W Swaan, S.H Wright. Molecular determinants of substrate/inhibitor binding

to the human and rabbit renal organic cation transporters hOCT2 and rbOCT2. Mol Pharmacol. 2005; 67: 1067-

1077.

[33] B. Hagenbuch, C. Gui. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP)

family. Xenobiotics. 2008; 38: 778-801.

[34] S.F Zhou. Structure, function and regulation of p-glycoprotein and its clinical relevance in drug disposition.

Xenobiotica. 2008; 38: 802-832.

[35] S.G Aller, J. Yu, A. Ward. Y. Weng, S. Chittaboina, R. Zhou, P.M Harell, Y.T Trinh, Q. Zhang, I.L Urbatch,

G.Chang. Structure of p-glycoproteins reveals a molecular basis for poly-specific drug binding. Science. 2009;323:

1718-1722.

[36] B. Stieger, Y. Meier, P.J Meier. The bile salt export pump. Pflugers Arch. 2007;453: 611-620.

[37] W.A Alrefai, R.K Gill. Bile acid transporters: Structure, function, regulation and pathophysiological

implications. Pharm. Res. 2007;24: 1803-1823.

[38] R.G Deelay, C. Westlake, S.P Cole. Transmembrane transport of endo and xenobiotics by mammalian ATPbinding

cassette multidrug resistance proteins. Physiol Rev. 2006; 86: 849-899.

[39] A.T Neis, D. Keppler. The apical conjugate efflux pump ABCC2 (MRP2). Pflugers Arch. 2007; 453: 643-659.

[40] P. Brost, C. de Wolf, K. van de Wetering. Multidrug resistance-associated proteins 3,4 and 5. Pflugers Arch.

2007; 453: 661-673.

[41] R.A Van Aubel, P.H Smeets, J.G Peters, R.J Bindels, F.G Russels. The MRP4/ABCC4 gene encodes a novel

apical organic anion transporter in human kidney proximal tubules: Putative efflux pump for urinary cAMP and

cGMP. J AmSoc Nephrol. 2002; 13: 595-603.

[42] R. Ganel, J.D.Rothstein. Ionotropic Glutamate Receptors in the CNS.Springer Berlin Heidelberg;1999.

[43] N.C.Danbolt. Glutamate Uptake. Prog Neurobiol. 2001; 65: 1-105.

[44] S. Holmseth, H.A. Scott, K. Real, K.P. Lehre, T.B. Leergaard, J.G.Bjaalie, N.C.Danbolt, The concentrations

and distributions of three C-terminal variants of the GLT1 (EAAT2:slc1a2) glutamate transporter protein in rat brain

tissue suggest differential regulation. Neuroscience. 2009; 162: 1055-71.

[45] D.V. Pow, N.L. Barnett. Developmental expression of excitatory amino acid transporter 5: a photoreceptor and

bipolar cell glutamate transporter in rat retina. Neurosci Lett. 2000; 280:21-4.

[46] T. Miyaji, N. Echigo, M. Haisa, S. Senoh, H. Omote, Y. Moriyama. Identification of vesicular aspartate

transporter. Proc Natl Acad Sci USA. 2008; 105: 11720-24.

[47] D.B. Shennan, I.D Miller, D.T Calvert. Mammary-tissue amino acid transport system. Proc Nutr Soc. 1997; 56:

117-191.

[48] V.K. Kansal, R.Sharma. Mechanism and regulation of amino acid transport in mammary glands: Review.

Asian-Aust J anim Sci. 2001; 14: 718-19.

[49] G.L. Amidon, G.D. Leesman, R.L. Elliot. Improving intestinal absorption of water-insoluble compounds: a

membrane metabolism strategy. J Pharm Sci. 1980;69: 1363-1368.

[50] V.J. Stella, K.J. Himmelstein. Prodrugs and site-specific drug delivery. J Med Chem. 1980; 23: 1275-1282.