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Pharmaceutical Sciences **Review Article……!!!**

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PRODRUGS:-A DEVELOPMENT OF CAPPING DRUGS

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INTRODUCTION

The term "prodrug" or "pro-agent" was first introduced in 1958 by Albert to describe compounds that undergo biotransformation prior to their therapeutic activity.[1] Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect.[2] According to IUPAC (International Union of pure and applied chemistry):Prodrug is defined as any compound that undergoes biotransformation before exhibiting its pharmacological effects. [3]such drug-derivatives have also been called 'latentiated drugs', 'bioreversible derivatives', and 'congeners', but 'prodrug' is now the most commonly accepted term. [4-6]In both drug discovery and development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents.[7,8] By applying prodrug technology, the clinical usefulness of a drug molecule may be enhanced without modifying the pharmacological activity of a parent drug. However, the design of an appropriate prodrug structure should ideally be considered at the early stages of preclinical development, bearing in mind that prodrugs, while not common, may alter the tissue distribution, efficacy and the toxicity of the parent drug. Moreover, promoieties used should ideally be safe and rapidly excreted from the body. The choice of promoiety should be considered with respect to the disease state, dose, and the duration of therapy. The prodrug approach can be exploited for almost all administration routes and dosage forms, and it can be applied to a wide variety of existing medicines on the market, as well as to novel drug molecules in the lead optimization step early in the drug discovery process.[9-11]

About 5–7% of drugs approved worldwide can be classified as prodrugs, and the implementation of a prodrug approach in the early stages of drug discovery is a growing trend[12-14]. The application of modern discovery technologies such as high-throughput screening and combinatorial chemistry can produce novel lead structures with high pharmacological potency, but the physicochemical and biopharmaceutical aspects of the initial leads have frequently been neglected. This can lead to drug candidates with poor drug-like properties that face significant problems later in drug development.[15] This is done to increase the usefulness of a drug by improve the physicochemical, biopharmaceutical or pharmacokinetic properties of the compound. By chemically modify an active agent various barriers can be overcome such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, toxicity, local irritation and change the physical form of drug. Prodrugs can also prolong the duration of drug action i.e. highly lipophilic prodrugs of

steroids and neuroleptics that are administrated intramuscular. In most cases the prodrug requires only one or two enzymatic or chemical transformations step to become the active drug. There are also so called co-drugs or mutual prodrugs where a prodrug consists of two pharmacologically active drugs, coupled together to act as a promoiety to each other[16,17]. A so called precursor prodrug does not contain a carrier or a promoiety but occurs after a molecule modification of the active agent itself i.e. oxidation or reduction. For example, prodrugs provide possibilities to overcome various barriers to drug formulation and delivery such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, toxicity and local irritation. Prodrugs can also improve drug targeting, and the development of a prodrug of an existing drug with improved physical and chemical properties may represent a life-cycle management opportunity. However, we have only begun to realize their full potential, and this is mainly due to the only recent understanding of various biological phenomena enabling the design of more sophisticated, safer and better-targeted prodrugs. With the aim of illustrating the full potential of the prodrug approach, this article will provide an overview of prodrug design, and then highlight the major applications of the prodrug strategy, including the ability to improve oral absorption and aqueous solubility, enhance lipophilicity and active transport, as well as achieve site selective delivery.

THE NEED OF PRODRUGS

A] Barrier related to physico-chemical properties of drug:

- Poor aqueous solubility – which being prevent the drug from administrated in the form of injectables.
- Low lipophilicity – which limits the design lipid bond formulation.
- Chemical instability – which prevent the drug to incorporate in to adequate forms.

B] Barriers in the pharmacokinetic phase:

- Incomplete absorption across biological membrane such as GIT mucosa & BBB.
- Low & variable bioavailability due to extensive first pass effect.
- Too rapid absorption or excretion when longer duration of the action is desired.
- Lack of site-specificity.
- Changes in organoleptic properties of active drug.

PRODRUG DESIGNING IS REQUIRING OVERCOMING THE FOLLOWING DRAWBACKS

- Unpleasant taste or odor.
- A wide range of adverse effect.

- Shorter duration of action.
- Instability.
- Site non-specificity.
- Poor absorption & distribution.
- Poor water solubility.
- Some compound are more active but unable to reach the site of action (e g. GABA).

Ideal properties of prodrug[18]:-

- ◆ It should not have intrinsic pharmacological activity.
- ◆ It should rapidly transfer chemically or enzymatically in to the active form where desire.
- ◆ The metabolic fragment apart from the active drug should be non-toxic.

Rationale and Considerations for the use of Prodrugs:-

This can be achieved through biological, physical or chemical means

- ◆ Prodrugs should be easily synthesized and purified. Elaborate synthetic schemes should be avoided because increased costs. Multistep syntheses increase operator time, decrease yield.
- ◆ Prodrugs must be stable in bulk form and dosage form.
- ◆ Neither the prodrug nor its metabolic derivatives should be toxic.
- ◆ The biological approach is to alter the route of administration which may or may not be acceptable to patient.
- ◆ The physical approach is to modify the design of dosage form such as controlled drug delivery of drug.
- ◆ The last and best approach in enhancing drug selectivity while minimizing toxicity, is the chemical approach for design of prodrugs.[19-21]

SOME CONSIDERATIONS FOR PRODRUG DESIGN[31]

The rational design of the prodrug can thus be divided into three basic steps:

1. Identification of the drug delivery problem.
2. Identification of the physicochemical properties required for optimal delivery.
3. Selection of a prodrug derivative that has the proper physicochemical properties and that will be cleaved in the desired biological compartment.

In this context it must be accepted that a very close collaboration is needed between the pharmaceutical chemists active in drug synthesis and those working in the area of xenobiotic metabolism. This is particularly important if more targeted prodrugs are designed in function of enzymes available at the right place, in the right amount, and with the right prodrug specificity.

TYPES OF PRODRUGS

Classification of prodrugs:-

I] On the basis of bioactivation site [22-23]**:-**

Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Acyclovir, 5-Flurouracil, Cyclophosphamide diphosphate, L-Dopa, Mitomycin C, Zidovudine
Type I	Intracellular	Type IB	Metabolic tissues (liver, GI mucosal cell, lung etc)	Carbamazepine, Captopril, Heroin, Paliperidone, Phenacetin,Primidone, Psilocybin,Suldinac,
Type II	Extracellular	Type IIA	GI fluids	Lisdexamfetamine, Loperamide oxide, Oxyphenisatin, Sulfasalazine
Type II	Extracellular	Type IIB	Systemic circulation and Other Extracellular Fluid Compartments	Acetylsalicylate,Bacampicillin, Chloramphenicol succinate,Dihydropyridine pralixoxime, Dipivefrin, Fosphenytoin
Type II	Extracellular	Type IIC	Therapeutic Target Tissues/Cells	ADEPTs, GDEPs, VDEPs

According tothis classification prodrugs can be classified into two major types, based on their cellular sites of bioactivation into the final active drug form.

1) Type I being those that are bioactivated intracellularly and
2) Type II being those that are bioactivated extracellularly, especially in digestive fluids or the systemic circulation

Both types can be further categorized into Subtypes, i.e.Type IA prodrugs include many antimicrobial and chemotherapy agents (e.g., 5-flurouracil).Type IB agents rely on metabolic enzymes, especially in hepatic cells, to bioactivate the prodrugs intracellularly to active drugs. Type II prodrugs are bioactivated extracelluarly, either in the milieu of GI fluids (Type IIA), within the systemic circulation and/or other extracellular fluid compartments (Type IIB), or near therapeutic target tissues/cells (Type IIC), relying on common enzymes such as esterases and phosphatases or target directed enzymes.

II] Depending upon constitution of the constitution, lipophilicity, method of bioactivation & catalyst involved

- Carrier linked Prodrugs
- Bioprecursor /Metabolic precursor
- Pro-prodrugs
- Mutual prodrugs

a) Carrier linked prodrug:

Prodrugs are the ones where the active drug is covalently linked to an inert carrier transport moiety. Such prodrugs have greatly modified lipophilicity due to the attached carrier and the active drug is released by hydrolytic cleavage, either chemically or enzymically.

It can be further subdivided into-

1) **Bipartate**:- Composed of one carrier (group) attached to the drugs.
2) **Tripartat**-:- Carrier group is attached via linker to drug. The carrier is not linked directly to the drug but instead through a linker. Allows for decreased steric hindrance during enzymatic cleavage that may occur with bipartate prodrugs
   • Carrier is enzymatically cleaved from Linker
   • Linker is spontaneously cleaves from Drug.

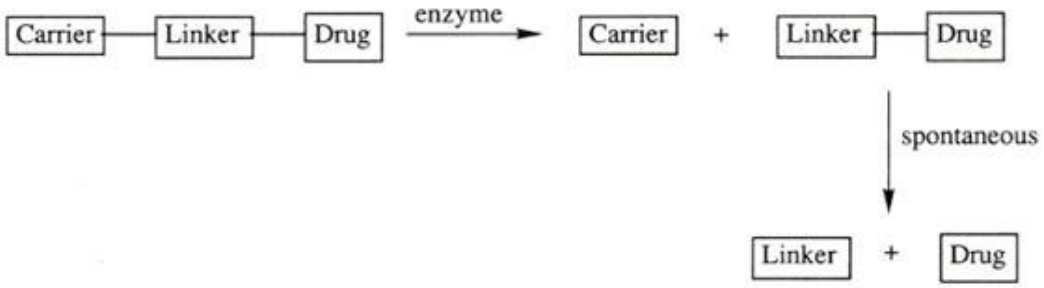
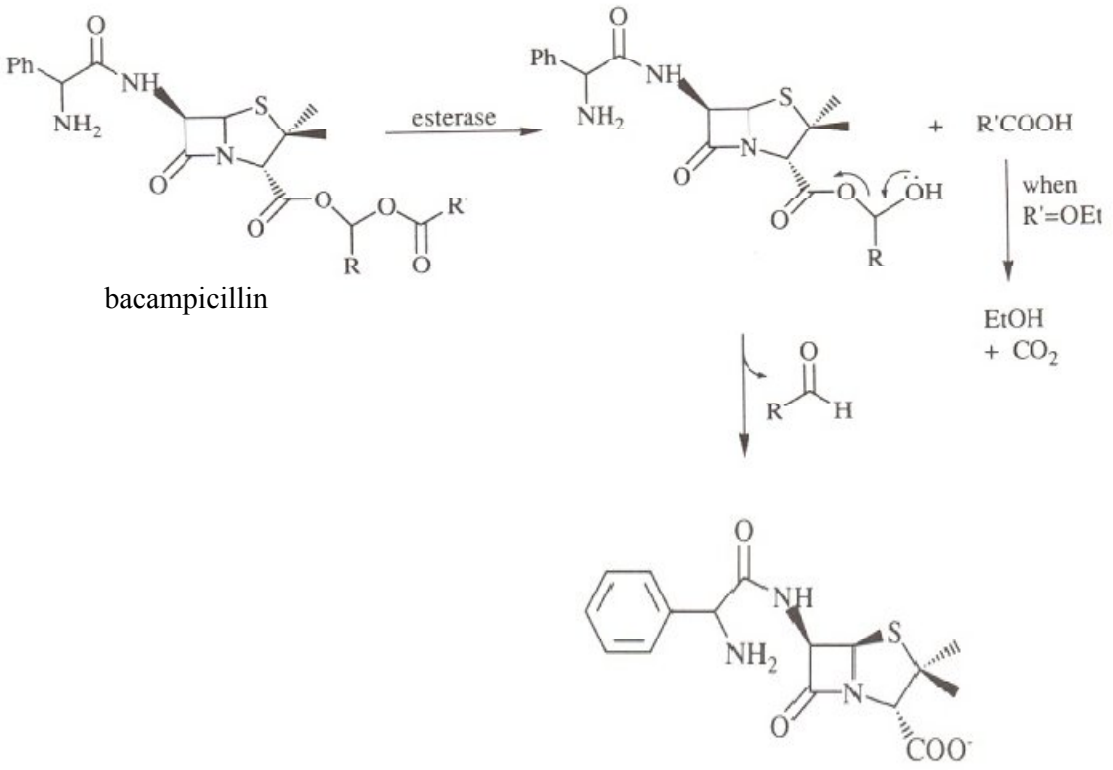


Fig: General strategy for bipartate and tripartat types of prodrugs.



bacampicillin

Ampicillin

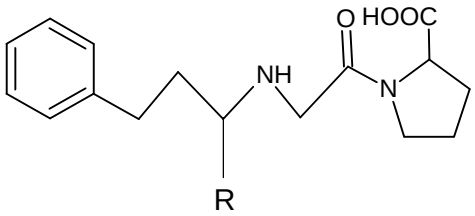
b) **Bioprecursors:**

Bioprecursors are inert molecules obtained by chemical modification of the active drug but do not contain a carrier. They metabolized into a new compound that may itself be active or further metabolized to an active metabolite. Such a moiety has almost the same lipophilicity as the parent drug and is bioactivated generally by redox biotransformation, only enzymatically.

E.g. 1) amine to aldehyde to carboxylic acid[28].

2) Fenbufen from aroyl propionic acid precursors.

3) Enalapril is prodrug of enalprilic acid.



R= $COOC_2H_5$ →Enalapril

R=COOH →Enalaprilic acid

Enalapril (Prodrug) →Enalaprilic acid (Active)

c] Mutual prodrugs:-

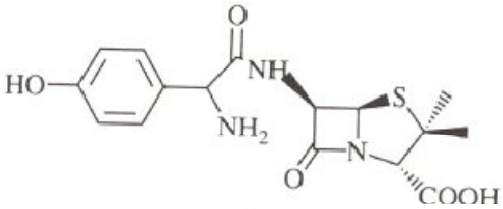
Where the prodrug comprises of two pharmacologically active agents coupled together to form a single molecule such that each acts as carrier for the other. Such prodrugs of two active compounds are called as mutual prodrugs.

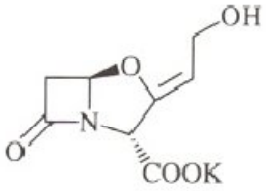
- Useful when 2 synergistic drugs need to be administered at the same site at the same time.
- Mutual prodrug is bipartate or tripartate where a synergistic drug acts as the carrier

E.g.1) Benorylate is mutual prodrug for aspirin and paracetamol.

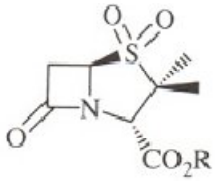
2) Sultamacillin:-.

Sultamacillin is a tripartate mutual prodrug (double ester) of ampicillin and penicillanic acid sulfone.

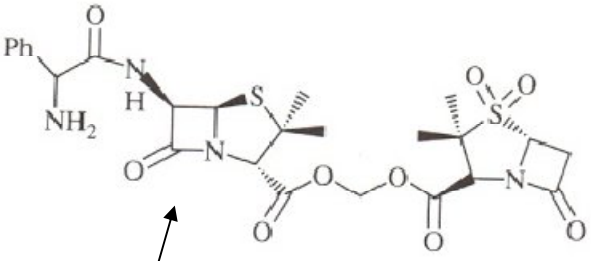




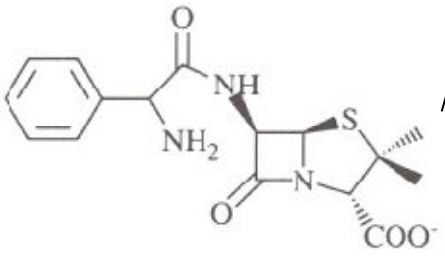
Ampicillin



penicillanic acid sulfone to treat β-lactamase producing bacteria

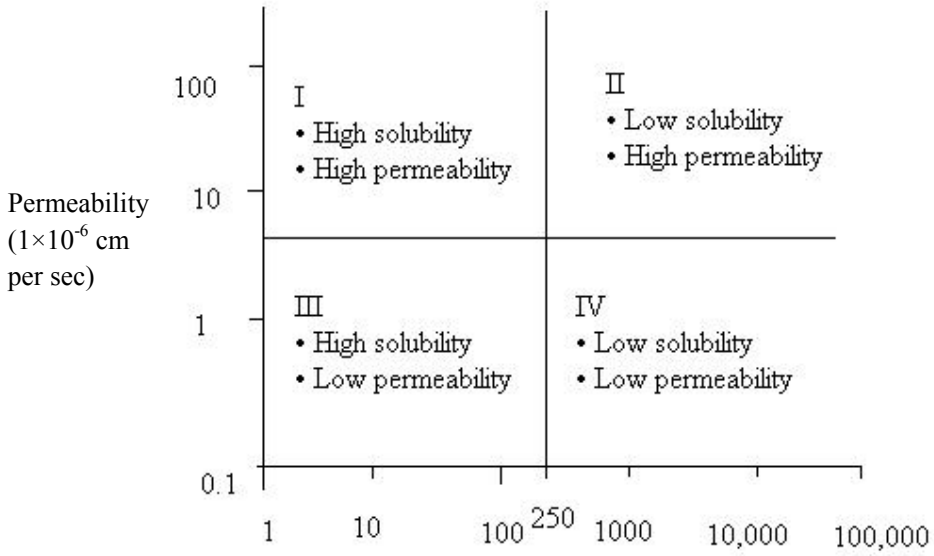


Sultamacillin
Absorbed, transported to the same site



III] Biopharmaceutical Classification System (BCS) characterization of drugs based on solubility and permeability measures[24]:-

a) High solubility High permeability
b) Low solubilityHigh permeability
c) High solubility Low permeability
d) Low solubility Low permeability



Many successful prodrugs are those of parent drugs from BCS Classes II and III. Prodrugs of BCS Class II parent drugs enhance solubility, whereas prodrugs of BCS Class III parent drugs are designed to enhance permeability. The x-axis shows the volume (ml) required to dissolve the highest dose strength of the parent drug at the lowest solubility over the pH 1–7.5. A parent drug is considered 'highly soluble' when the highest dose strength is soluble in <250 ml water over a pH range of 1–7.5, in which 250 ml reflects the so-called FDA glass of water. Permeability is defined by various in vivo or in vitro assays, and a permeable drug is one associated with ≥90% oral bioavailability or ≥90% absorption as assessed by urinary excretion data.

Application of Prodrug –

1] **Pharmaceutical Application**:

1. Improvement of taste.
2. Improvement of odour.
3. Change of physical form for preparation of solid dosage forms.
4. Reduction of pain on injection[25-27].
5. Enhancement of drug solubility and dissolution rate.

6. Enhancement of chemical stability of drug.
7. Reduction of GI irritation.

2] Pharmacokinetic application:

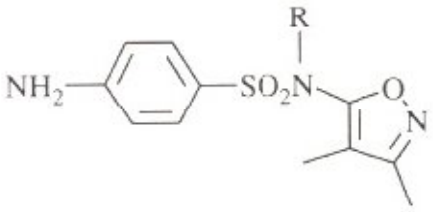
1. Enhancement of bioavailability (lipophilicity),
2. Prevention of presystemic metabolism,
3. Prolongation of duration of action,
4. Reduction of toxicity,
5. Site-specific drug delivery.

1) Improvement of Taste

Taste is an important parameter in case of drugs administering orally. Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. The problem of bitter taste of drug in pediatric formulations is a challenge to the formulators in the present scenario. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which inturn decides the commercial success of the product. Although not directly related to the physiological process of absorption, it may happen that oral drugs with a markedly bitter taste may lead to poor compliance if administered as a solution, syrup, or an elixir.

E.g.1) Chloramphenicol Oral administration is limited for most of these compounds and systemic availability can be substantially improved by sublingual dosing. However, discomfort ascribed to bitter taste is a common complaint from patients administered morphine or similar compounds buccally. Many prodrugs of these analgesics or their antagonists do not taste bitter and may represent an attractive alternative to injections when the oral route is not adequate because of low systemic availability.

2) Sulfa drug: pediatric antibiotics, bitter taste (R=H) When R=CH3CO, tastless



2) Improvement in the Shelf Life of Parenterals:-

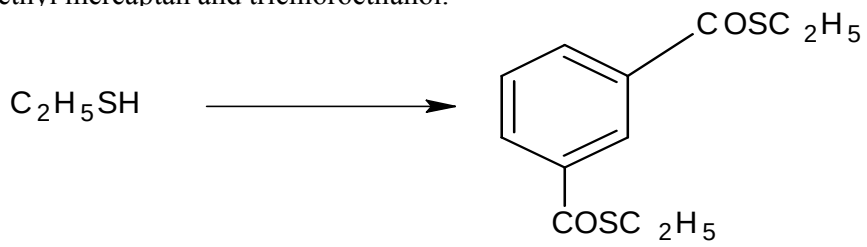
For a prodrug, the true utilization time has been defined as the time during which the total concentration of prodrug and drug equals or exceeds 90% of the original prodrug concentration. It has consequently been argued that the storage of active ingredients in solutions as prodrugs

might produce advantages . If it is assumed that a solution of the parent drug is useful until its concentration decreases to 90% of its initial value, a prodrug utilization time can be defined as the time during which administration of the prodrug provides a bioavailable dose of drug equal to or better than the parent drug at . Under optimal conditions, of the prodrug might be rather longer than for the active moiety stored as such. Caution must be used, however, because this concept is valid only if the prodrug degrades to the active principle and if the given definition is considered valid for the drug product under scrutiny. A problem arises when a prodrug in solution prematurely converts to the drug through chemical hydrolysis during storage and simultaneously to an inactive product through a degradation pathway similar to that of the parent drug. For example, hydrolysis of ester prodrugs of penicillins may yield the corresponding penicillins while simultaneously forming inactive p-lactam degradation products.

3) CHANGE IN PHYSICAL FORM OF DRUG:-

Some drugs which are in liquid form, are unsuitable for formulation as a tablet especially if their dose is high.The method of converting such liquid drugs into solid prodrugs involves formation of symmetrical molecules having a higher tendency to crystallize.

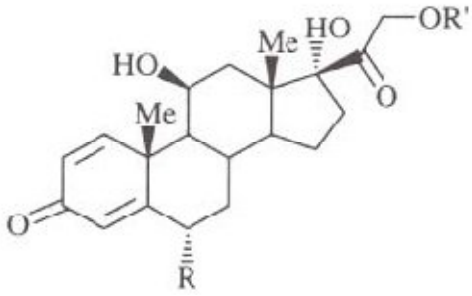
e.g. Esters of ethyl mercaptan and trichloroethanol.



ethyl mercaptan 1-3-diester **1-3-diester**

4) Prodrugs for Increased Water Solubility.

Prednisolone and methylprednisolone are poorly water-soluble corticosteroid drugs. For aqueous injection or ophthalmic delivery they must be converted to water soluble prodrugs.

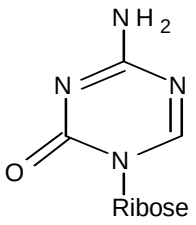


R = H	R'=H	predinsolone
R = CH3	R'=H	methylprednisolone

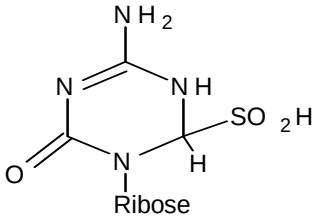
5) Enhancement of chemical stability:

A drug may stabilize either during its selflife or in the GIT when used orally. Selflife stability is particularly important in case of the drug for I.V. use. The convential approach is to lyophilize such solution in to powder which can be reconstituted before use. The prodrug design of such agent is also a good alterative to improve stability.

E.g. The aqueous solution of anti-neoplastic drug azacytidine is readily hydrolyzed but the bisulfite prodrug is stable to such as degradation at acidic PH & is more water soluble than the parent drug. The prodrug converts to the active drug at the physiological P^H of 7.4



Azacytidine



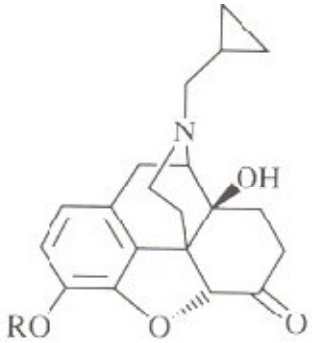
Stable bisulfite prodrug

6) Prodrugs for Stability

Prodrugs may protect a drug from *1st-pass effects*.

E.g. 1) Propranolol (antihypertensive drug) suffers from first-pass elimination resulting in decreased bioavailability of oral doses compared to i.v. injections. One of the major metabolites is the O-glucuronide. The hemisuccinate ester was designed to block glucuronide formation resulting in an 8-fold increase of plasma levels of propranolol.

2) Naltrexone (R= H):- Not stable in the first pass



R= CO-*o*-NO2Ph, anthranilate (o-nitrobenzoate) bioavailability 45 times.

R= CO-*o*-AcOPh, acetylsalicylate bioavailability 28 times.

1) Improved oral absorption

Maximal oral absorption is a function of three factors;

- The fraction of dose absorbed
- The fraction of dose escaping intestinal metabolism
- The fraction of dose escaping hepatic metabolism

For the majority of drugs, the bioavailability is balanced by oral absorption and clearance. These in turn, are controlled by the physiochemical parameters of the drug or prodrug; GI permeability, solubility, dissolution and dosage. Some prodrugs overcome poor absorption in parent drug by enhancing permeability.

E.g. masking polar/charged features in parent drug:-

The intestinal absorption of a drug could be limited by efflux transporters through secretion drugs and intracellular metabolites back into the intestinal lumen. If the first-pass metabolism is low to moderate and it is not the main limitation of drug availability, then prodrugs can improve aqueous solubility and thus the bioavailability. This often achieved by adding an ionizable progroup to parent drug. The most frequent usage of prodrugs is to mask polarity and ionizable groups to improve oral bioavailability. By increasing the lipophilicity, the membrane permeability is promoted. The prodrugs that target certain receptors are designed with structural features that increase the receptor affinity of the drug. This is important for polar/charged drugs that experience none passive transport.

2) Improved parenteral administration

One of the biggest advantages of adding promoieties to parenteral drugs is that it can increase the solubility of the drug greatly, sometimes by thousands or tens of thousands. This means that the total volume of the drug needed to gain the desired effect is greatly reduced, which in turn leads to shortening of the time needed to administer the proper dose. There are numerous successful prodrugs with improved aqueous solubility properties for parenteral administration. The most commonly used prodrug-based approach to increase water solubility is to introduce an ionizable/ polar promoiety to the parent drug. As the increase in solubility imparted by the dianionic phosphate group is often of several orders of magnitude, several phosphoric acid esters have been developed as potential water-soluble prodrugs for parenteral administration and, less commonly, for oral administration.

a) **Improved topical administration:-**

The topical administration of drugs encompasses all external membranes, but here we consider only ocular and dermal prodrug applications. Administering drugs topically often poses some

difficulties. One of the target areas for topical drugs is the cornea, but the cornea is not very permeable to normal drugs. Mostly as much as 50-99% of the drug administered end up in the bloodstream instead of the eye. Adding the proper promoiety increases the drugs fat solubility, making it more permeable to the cornea and shortening the time it takes to administer the right dose by a factor of almost 20 times. Another area that is tough to apply to is the skin. Mostly, to be able to permeate the outer skin (*stratum corneum*) the drug needs to be either highly lipophilic or highly hydrophilic. Numerous studies have demonstrated that both water and lipid solubilities, and/or a balance of the two, are important in the optimization of drug permeation. These optimal features can often be achieved by prodrugs.

By adding a promoiety that makes the drug lipophilic, which then is rapidly metabolized once it enters the body, the drug will be able to enter the body rapidly without accumulating in the fatty tissue under the skin. Another aspect of prodrugs is the ability to be target specific, to ensure that the drug only affects the tissue that you want to treat. This ability is useful in any kind of medical treatment, but will be especially handy when treating tumors, or the central nervous system. There are several ways to make a drug target specific. One is to design the drug so that only the targeted tissue is able to absorb the drug. Another way is to attach the parent drug to a transport molecule or marker molecule that is similar to those used by the body. Another interesting possibility is to administer the drug in an inactive form which can reach the desired tissue and once it gets there is activated by enzymes specific to that tissue only.

E.g. In the case of tazarotene its active carboxylic acid form is esterified to a more lipophilic ethyl ester, which still maintains adequate water solubility. Tazarotene was effectively and reliably absorbed percutaneously, exerted less skin irritation and was rapidly converted to tazarotenic acid. The less lipophilic tazarotenic acid subsequently released, showed no accumulation in fat and other tissues in part due to the reduced systemic half-life of this parent drug, achieved by the introduction of a metabolically labile sulphur group that undergoes rapid oxidative deactivation and thus prevents accumulation in tissues. Thus, tazarotene is not only a carboxylic acid prodrug with enhanced skin permeability, it is also a soft drug with enhanced systemic metabolism. Both can be important features for drugs aimed at topical treatment.

b) **Ophthalmic drug delivery**:-

A major challenge in ocular therapeutics is improving the poor local availability of topically applied ophthalmic drugs. The corneal barrier limits the permeation of topically administered ophthalmic drugs into the intraocular tissues. As a result, only a small percentage of the applied dose is absorbed, most (50–99%) of which escapes into the systemic circulation.

During the past decades, considerable effort has been devoted to prolonging precorneal drug retention through vehicle manipulations (viscosity, polymeric inserts), with the hope of enhancing ocular availability. Thus far, it seems that such methods have only resulted in moderate success. This is probably attributable to the modest improvement in ocular drug availability as exemplified by viscous solutions and by the lack of patient acceptance of, for example, inserts. Approaches to enhance corneal drug permeability:

a) Modification of the *integrity of the corneal epithelium* transiently by use of penetration enhancers.

b) Modification of *thephysicochemical characteristics of the drugproduct* through ion-pairformation.

c) Modification of the *physicochemical characteristics of the active principle* by prodrug derivatization.

However, thus far, only the prodrug approach seems to have met objectives that allow commercialization of such ophthalmic products.

Site specificity:

The most important feature of efficient drug is right site of action. It is necessary to deliver the drug precisely to the affected part of body, where it is supposed to be attacked.

• At least three following factors should be optimized to obtain a prodrug acting at specific site:-

1) Prodrug must be directly transported to the site of action, and uptake at the site must be rapid and essentially perfusion rate must be limited.

2) Once the prodrug reaches the site of its action, it must be selectively cleaved yielding the active drug, relative to its conversion at other sites.

3) Once selectively generated at site of action, the active drug must be retained by tissue.[2]

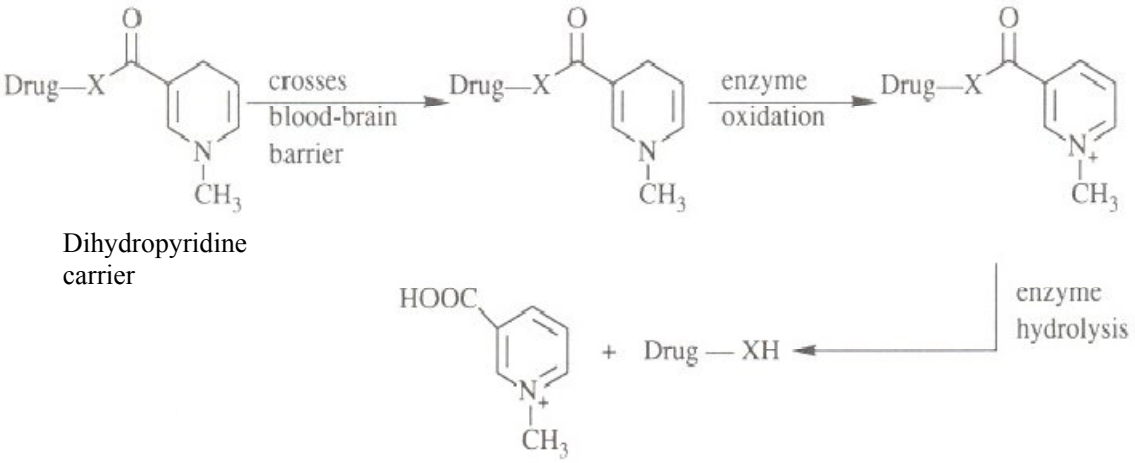
Solution-

These problems can be overcome by:

- Targeting the drug to its site of action by altering its disposition characteristic.
- There are several approaches to drug targeting and prodrug design is one of them.[30]

E.g. 1) Oxyphenisatin is a bowel sterilant that is only active when administered rectally. Acetylation (protection) of the hydroxyls allows the drug to be administered orally which is then hydrolyzed at the desired site of action, the intestines.

2) Bodor & coworkers developed a reversible redox drug delivery system for getting drugs into the CNS.



non-toxic carrier easily eliminated from brain

Prodrugs in ADEPT,GDEPT and VDEPT

A prodrug in ADEPT must fulfil a number of conditions to be applicable. Important characteristics for a prodrug are:

- reduced toxicity compared to the parent drug,
- stability in serum,
- efficient enzymatic activation only by the targeted enzymes, and
- low cellular uptake.

A large number of prodrugs designed for use in ADEPT but the major obstacles, however, for the use of most of the prodrugs in ADEPT are:

- too slow activation rate by the matching enzyme
- premature prodrug activation by endogenous enzymes
- too high toxicity ofthe prodrug.

The activation of specially designed prodrugs by antibody-enzyme conjugates targeted to tumor -associated antigens is another form of the use of antibodies in cancer therapy. [32,33]A substrate group for a given enzyme is coupled directly to a cytotoxic drug. Upon contact of the prodrug with the matching enzyme, the drug is generated. The group which is a substrate for the enzyme is referred to as the specifier group. A problem encountered in this type of prodrug is a too slow enzymatic activation rate. In most cases, this was attributed to steric hindrance of the prodrug on the enzymatic scission reaction. In ADEPT and VDEPT, the preferred targets may be the enzymes of nonhuman or non mammalian origin that could catalyze substrates not normally activated in humans. Thus, in terms of specificity, enzymes from nonhuman sources, particularly those of microbiological origin, are advantageous, and if their immunogenicity is

controllable, then specificity may become the overriding consideration. In contrast, charged prodrugs that are bifunctional alkylating agents are especially suitable for ADEPT[33]. Because of the charge, they will not enter cellsand are nontoxic because the essential target for alkylating agents is intracellular DNA. After extracellular activation of prodrugs in tumor cells, the active drug will be freely diffusible and attain a high intracellular concentration.

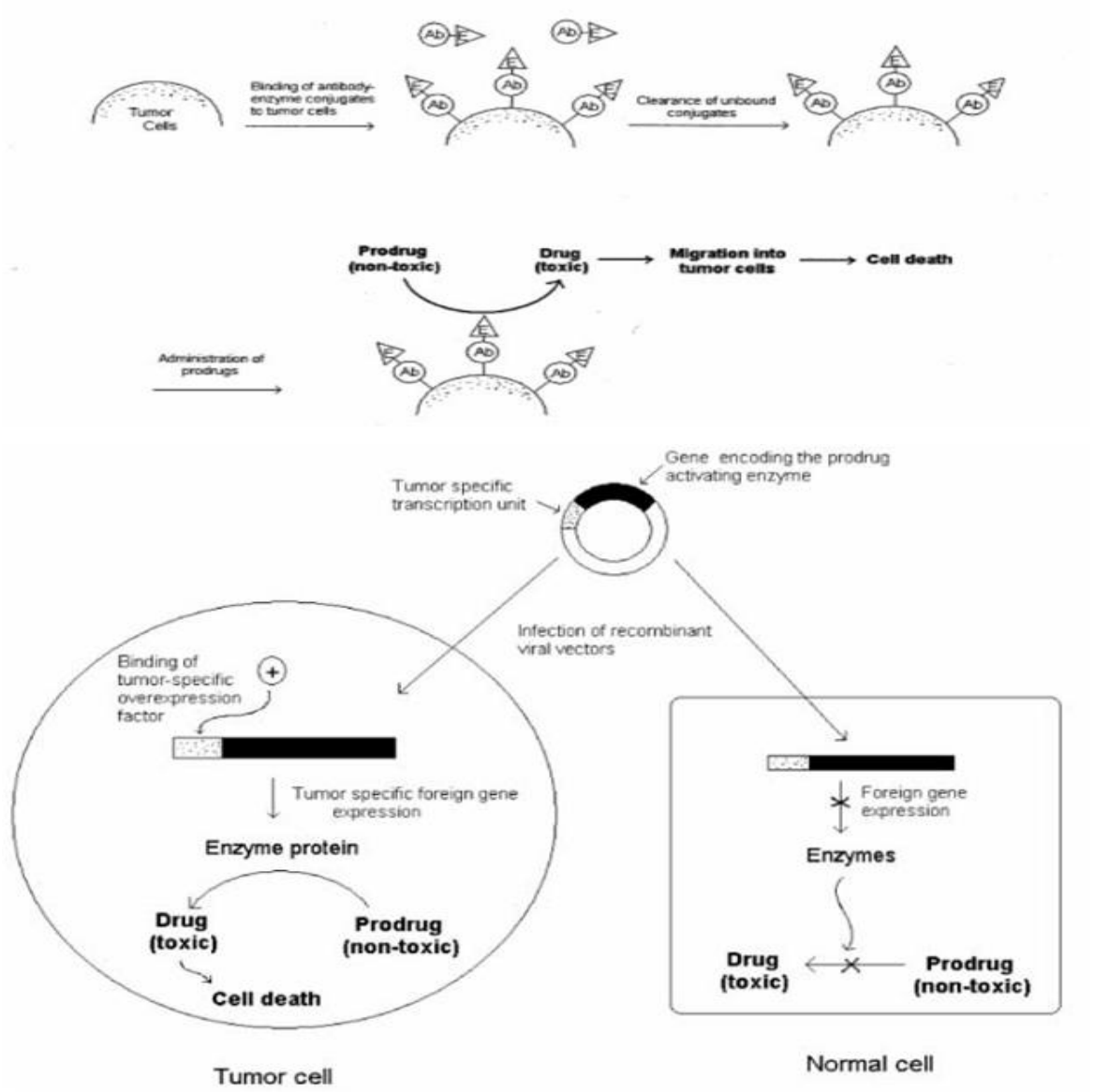


Fig: Schematic representation of ADEPT and VDEPT.

CONCLUSIONS

Although prodrug design started more than 30 years ago and many reviews have been written on this subject, very little information is available in official guidelines or pharmacokinetic textbooks on the regulatory requirements or data analysis for this type of compounds. The

present review is an attempt to gather and confront available information on the subject. It is clear from the foregoing, that the development of prodrugs promises to be a very effective method for treatment of diseases in the future. This approach has several advantages over conventional drug administration. Site specificity is central to the prodrug development strategy. Even though at present prodrugs are not prevalent in clinical use, in future there will be prodrugs for every known drug to make them effective in treatment. Drug discovery and prodrug development appear to be complementary for the generation of target specific medicines of future. At present the research in this area is at a nascent stage due to lack of information regarding all the enzymes or receptors most suitable for targeting purposes. As the unravelling of the micro biological details of affected targets become clear, prodrug development will surely decrease side/toxic effects of drugs and also trigger development of more potent primary drugs.

REFERENCES

1. Albert A. Chemical aspects of selective toxicity. Nature. 1958;182:421-423. Harper NJ. Drug latentiation. Prog Drug Res. 1962;4:221-294.
2. Tripathi K.D. Essentials of medical pharmacology.4th edition , 25.
3. IUPAC Pure and appl. chem.,1998,70,1129-1143
4. Roche EB. Design of Biopharmaceutical Properties through Prodrugs and Analogs. Washington, DC: American Pharmaceutical Association; 1977.
5. Sinkula AA, Yalkowsky SH. Rationale for design of biologically reversible drug derivatives: prodrugs. J Pharm Sci. 1975;64:181-210.
6. Stella VJ, Charman WN, Naringrekar VH. Prodrugs. Drugs. 1985;29:455-473.
7. Stella, V. in Optimizing the "Drug-Like" Properties of Leads in Drug Discovery (eds Borchardt, R., Hageman, M., Stevens, 221–242 (Springer, New York, 2006).
8. Beaumont, K., Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. Curr. Drug Metab. 4, 461–485 (2003).
9. V. J. Stella, M. J. Hageman, R. Oliyai, H. Maag, and J. W. Tilley. Prodrugs: Challenges and Rewards. Vol. 1–2. Published by AAPS Press and Springer, New York, (2007).
10. T. Järvinen, Design and pharmaceutical applications of prodrugs. In S. Gad (ed.), Drug discovery handbook. John Wiley & Sons, Inc., Hoboken, 2005, pp. 733–796.
11. K. Beaumont, Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: Challenges to discovery scientist. Curr. Drug Metab. 4(6):461–485 (2003), Dec.
12. Ettmayer, P., Amidon, G. L., Clement, B. & Testa, B. Lessons learned from marketed and investigational prodrugs. J. Med. Chem. 47, 2393–2404 (2004).

13. Jarvinen, T., Drug Discovery Handbook (ed. Gad, S.) 733–796 (John Wiley 2005).
14. Stella, V. J. Prodrugs as therapeutics. Expert Opin. Ther. Pat. 14, 277–280 (2004).
15. Venkatesh, S. & Lipper, R. A. Role of the development scientist in compound lead selection and optimization. J. Pharm. Sci. 89, 145–154 (2000).
16. Kiptoo, P. K., Hamad, M. O., Enhancement of transdermal delivery of 6-b-naltrexol via a codrug linked to hydroxybupropion. J. Control. Release 113, 137–145 (2006).
17. Leppanen, J. Design and synthesis of a novel l-DOPA-entacapone codrug. J. Med. Chem. 45, 1379–1382 (2002).
18. D. M. Bramhmankar, S.B. Jaiswal, "Biopharmaceutics and pharmacokinetics A Treatise",1st Edition, Vallabh prakashan, Page No.159-176
19. Robinson R.Joseph, Lee Vincent H.L., Controlled Drug Delivery fundamental and application , 2nd edition, 337-369.
20. http://www.ingentaconnet.com/content/maik/biry/2002/000000067/00000010/0
21. Bahl C.R., Primplaskan H.K., Sileno A.P., Demeireles J., Vol 29,1-2, 5Jan,1998,89-116
22. Wu,K.M.,Classification of Prodrugs:Regulatory Perspectives Pharmaceuticals2:77-81, 2009.
23. Dependent Toxicity Management: Nonclinical Pharm/Tox Analysis and the Role of Comparative Toxicology. Toxicology 2007, 236, 1–6.
24. Mayer D.L., Jungheim L.N, Law K.L., Mikolajczyle S.D., Shapherd T.A., Cancer Res.,1993, sep.1:53(17):3956-63.
25. S. Kenneth, Prodrug topical and ocular drug delivery,17- 22.
26. www.Pharm-today.com/uploads/media/files/ prodrug- 20080425-185
27. http://userwww.sfsu.edu/~cberkman/640-notes-1.5pdf
28. Friend D.R.,Chang G .W,J. Med chem.,1984,27,261-266
29. Kawakami S.,Yamishita.F., Adv. Drug Delivery Review,Vol 45,Issue 1, 6 dec 2000,77-88.
30. Duvaz, L. Davies, and C. J. Springer, Anticancer Drug Des., 14, 517 (1999).
31. K. N. Syrigos and A. A. Epenetos, Anticancer Res., 19,605 (1999).
32. WJ, Pinedo HM. A monoclonal antibody-ß-glucuronidase conjugate as activator of the prodrug epirubicin for specific treatment of cancer. Br J Cancer. 1992;66:474-478.