



## PRODRUGS: LEGENDARY 'MAGIC BULLETS' FOR DELIVERY OF THERAPEUTICS

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### ABSTRACT

The prodrug approach has become an extensive tool to prevent a myriad of undesirable biopharmaceutical properties like minimal oral absorption, permeability, toxicity, and excessive first pass metabolism, physicochemical properties like poor solubility, chemical instability, bad odour or taste, or pharmacodynamic properties like irritation or pain and promises to be very effective for treatment of many diseases in future. Targeted drug delivery by the prodrugs is one of the biggest goals currently challenging the pharmaceutical and formulation scientists. The future potential of prodrugs is very immense, enabling multimechanistic drug targeting approaches, and they may prove to be the legendary "magic bullets" for delivery of therapeutics. This review provides insight into various prodrug strategies explored to date for drug delivery to various sites. Several examples of where the prodrug approach has been used to achieve targeted delivery will be discussed.

**Keywords:** Prodrugs, Barriers, Drug Targeting, Drug Delivery.

### INTRODUCTION

It is a well known fact that nearly all the therapeutic drugs possess different biological and physico-chemical characteristics that may be either desirable or undesirable. These undesirable characteristics may act as the bio-pharmaceutical or pharmacokinetic and pharmacological barriers to drug's usefulness. A large number of drug discovery scientists are carrying out the research activities for discovering the methods that are directed at reducing the undesirable characteristics and improving the therapeutic efficacy of the therapeutically significant drugs while retaining the desirable characteristics.<sup>1,2</sup>

Poor permeability (acetaminophen, theophylline), minimal solubility (corticosteroids), chemical instability (dopamine, acyl glucuronides), limited bioavailability (ampicillin), lack of site specificity (antineoplastic agents), toxicity (propanaldehyde, amphetamines), low or incomplete drug absorption (epinephrine), poor patient acceptance (chloramphenicol) and poor targeting capabilities are some of the undesirable characteristics of the drugs that plague the drug discovery and development.<sup>3</sup> Normally, in most of the drugs with poor targeting capabilities, only a small amount of the drug reaches the targeted site, whereas the remaining amount of the drug reaches to the other non-targeted sites which leads to undesirable side effects and inefficient drug delivery.<sup>4</sup>

The efficacy of the therapeutically significant drugs can be achieved through:

1. The biological approach, where the route of administration of the drug is altered. The versatility of

this approach is severely limited as the alternative routes of administration are less convenient than the oral route. For example, injectable route is used to optimize the onset of action, reduce gastric irritation and maximize bioavailability. But the levels of acceptability of the patient vary.

- The physical approach where the design of the drug dosage form could be modified as in the case of the controlled release and modified release drug dosage forms. Augmentin XR (GlaxoSmithKline), Cipro XR (Bayer) and Procardia XL (Pfizer) are the controlled release dosage forms of Amoxicillin/ Clavulanate potassium, ciprofloxacin and nifedipine respectively. In the case of Procardia XL, the drug is formulated as OROS (Oral osmotic pump) tablets, where the release of the drug nifedipine is controlled carefully and is not influenced by the gastro-intestinal conditions such as GI motility and pH.<sup>5,6</sup>
- The chemical approach involves the design of Prodrugs whose main objective is to convert an active molecule of interest into a drug that is clinically acceptable. This enhances the selectivity of the drug while limiting the toxicity. The chemical approach is the best of all and the targeted Prodrug design represents a new strategy for directed and efficient drug delivery.

### PRODRUGS

The concept of Prodrugs dates back to late 1950s, when Albert (1958) first introduced the term 'prodrug' or 'proagent' in his article in Nature to signify the compounds that undergo biotransformation prior to exhibiting the pharmacological effects.<sup>7</sup> Later, these



compounds have been referred to as the ‘latentiated drugs’ and the process as ‘drug latentiation’ by Harper, which he described as the chemical modification of a biologically active compound to form a new compound which, upon in vivo enzymatic attack liberates the parent compound. These compounds were also called as ‘congeners’ and ‘bioreversible derivatives’.<sup>8-13</sup>

Prodrugs can be defined as the pharmacologically inactive molecules which require an enzymatic or non-enzymatic transformation to release the active parent drug in vivo to exert a therapeutic effect that occurs prior to, during or after the absorption or in the specific target tissues.<sup>14,15</sup>

The rationale for the prodrug design is mainly to achieve a myriad of favourable biopharmaceutical properties like oral absorption, permeability, toxicity, and first pass metabolism, physicochemical properties like solubility, chemical stability, odour or taste, or pharmacodynamic properties like reduced irritation or pain<sup>16-18</sup> and prevent the barriers that plague the drug discovery and development. Figure 1.<sup>19</sup>

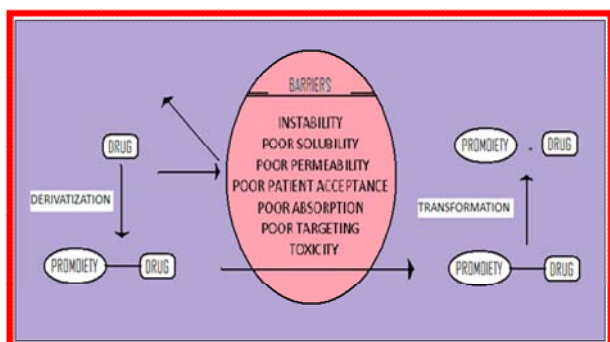


Figure 1: Prodrug Concept (Prodrug = Promoiety + Drug)

Prodrugs may exist either naturally or can be obtained through some synthetic or semi-synthetic processes.

1. Natural: Various phytochemicals and endogenous substances.
2. Synthetic or semi-synthetic: These are of two types.
  - a. Prodrugs existing naturally or produced fortuitously during drug development: Aspirin, codeine, heroin, psilocybin, irinotecan, and L-dopa
  - b. Prodrugs resulted through strategically targeted rational drug design: Oseltamivir (Tamiflu), ACE Inhibitors (Lisinopril, Enalapril), NSAIDs (Diclofenac), Antibiotics (Sarmoxicillin, Bacampicillin).<sup>20</sup>

A prodrug is said to be ideal if it has optimal physicochemical properties like solubility, permeability, lipophilicity, stability in GI tract and if the promoiety is non-toxic and releases the active drug at an appropriate rate *in vivo*.<sup>21</sup>

**Classification of Prodrugs**

This classification of Prodrugs<sup>20</sup> is based on the site and tissue location of conversion of the prodrug. (TABLE 1)

**DRUG TARGETING OR SITE-SELECTED DRUG DELIVERY**

Targeted or site-specific or site-selective drug delivery, the ultimate aim of all drug delivery research scientists, results in an optimal therapeutic benefit of a drug and minimizes the undesired effects. Targeted drug delivery could be achieved by enhancing the availability of drug at the targeted or response site besides reducing its availability at the non-targeted sites.

Table 1: Classification of prodrugs

TYPE AND SITE OF CONVERSION	SUBTYPE AND TISSUE LOCATION OF CONVERSION	EXAMPLES
<b>I Intracellular</b>	I A Therapeutic target tissues/ cells	Cyclophosphamide, Acyclovir, L-Dopa, Mitomycine-C
	I B Metabolic tissues Liver, GI mucosal cells, lung	Carbamazepine, Captopril, Heroin, Psilocybin, Phenacetin, suldinac.
<b>II Extracellular</b>	II A GI fluids	Lisdexamfetamine, loperamide, Oxyphenisatin, sulfasalazine.
	II B Systemic circulation and extracellular fluid compartments	Bambuterol, Fosphenytoin, Acetylsalicylate, Bacampicillin.
	II C Therapeutic target tissues/ cells	ADEPs, GDEPs, VDEPs

Therapeutic advantage and drug targeting index are the parameters that assess the efficiency of drug targeting. Therapeutic index (a) of a drug is the ratio of the maximum tolerated dose to the minimum effective dose, whereas the therapeutic advantage (b) is an assessment of the benefits of targeting in relation to the therapeutic indices of the targeted and non-targeted drug. Drug targeting index (c) is an indicator of pharmacological

efficiency and toxicity of a targeted delivery system and serves as a measure of quantitative gain associated with targeting. In this concept, it is assumed that area under the curve (AUC) reflects the pharmacological activity and the toxicity of the drug. It is defined as the ratio of the ratio of drug delivered to targeted and toxic sites when employing targeted delivery system to the same ratio when non-targeted delivery system is employed.<sup>22, 23</sup>



- a) Therapeutic Index =  $\frac{\text{Maximum Tolerated Dose}}{\text{Minimum Effective Dose}}$
- b) Therapeutic Advantage =  $\frac{\text{Therapeutic Index}_{\text{targeted drug}}}{\text{Therapeutic Index}_{\text{non-targeted drug}}}$
- c) Drug Targeting Index =  $\frac{(\text{AUC}_{\text{targeted site}} / \text{AUC}_{\text{toxic site}})_{\text{targeted drug}}}{(\text{AUC}_{\text{targeted site}} / \text{AUC}_{\text{toxic site}})_{\text{non-targeted drug}}}$

If the D. T. I values are greater than 1; it reflects a benefit from the use of a targeted delivery system. Drug targeting increases the high local concentrations of a drug at the targeted site and hence alleviates the dose-limiting side-effects. This phenomenon is especially desirable for highly toxic drugs, such as those employed in the treatment of cancer and also for the drugs with a narrow therapeutic window.<sup>22, 23</sup>

### PRODRUGS FOR SITE-SELECTIVE DRUG DELIVERY

Site-selective drug delivery is achieved by passive drug enrichment of the drug in the organ by selective metabolic activation through enzymes, and by antigen targeting, via transporter mediated delivery.<sup>24, 25</sup>

The factors that must be optimized for obtaining prodrug acting at specific site are:

- The prodrug must be transported to the site of action directly and must undergo a rapid uptake. There must be a limited rate of perfusion.
- On reaching the site of action, it must be cleaved selectively by yielding the active drug, relative to its conversion at other sites.
- The active drug must be retained by tissue, once selectively generated at the site of action.<sup>26, 27</sup>

### CNS – Targeted Drug Delivery

The development of new drugs for the Central Nervous system has not kept pace with progress in the molecular neurosciences as the majority of new drugs discovered do not cross the Blood-Brain Barrier (BBB), which is the main challenge to the transport of drugs to the Central Nervous System. It is often possible to achieve enhanced CNS delivery and limit the side effects in other tissues or organs by having knowledge of the specific transport mechanisms and enzymatic activity at the BBB and CNS.

In order to increase the concentration of the drug in CNS, the lipophilicity of the parent drug has to be increased. When the lipophilicity of the drug is increased via a prodrug, it will exhibit an enhanced penetration into the CNS. Besides increasing the lipophilicity, it must be ensured that the target tissue bioconversion is rapid and selective enough for competing with elimination from target tissue.<sup>27, 28</sup>

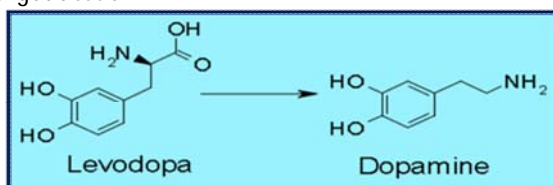


Figure 2: Bioconversion of Levodopa to Dopamine

One of the best examples that is considered as a prodrug and achieves targeted delivery into central dopaminergic neurons is Levodopa (Dopar). LAT1 is a neutral amino acid transporter expressed at the BBB. Levodopa is a substrate of LAT1. This uptake transporter carries Levodopa to brain tissue and Levodopa rapidly gets converted to dopamine by the enzymes present only in the nerves. After the bioconversion, (Figure 2) a very hydrophilic dopamine is trapped into the CNS, enabling its pharmacodynamic effects selectively in brain tissue.

### Cancer-Targeted Drug Delivery

Cancer is now one of the principal causes of death in the western world, except for heart and coronary disease. The average chance of being cured of cancer is augmented by only 0.5 percent, though there had been an extensive cancer research to find improved drugs and treatments. Most of the chemotherapeutic agents that are used for cancer treatment have a very small therapeutic window or index, which indicates a little therapeutic effect, while they cause severe, sometimes life-threatening side effects. Cancer is a group of diseases characterized by uncontrolled and independent proliferative growth of tumor cells.<sup>29</sup>

Lack of selectivity of chemotherapeutic agents is a major problem in cancer treatment. Hence there is a necessity of developing targeted delivery approaches for chemotherapeutic agents. The aim of cancer therapy is to target an inactive prodrug selectively to tumor cells where the active drug is released without being toxic to normal, healthy tissue. Because of the very high proliferation rates of tumor cells, in addition to the bioreductive activity, certain enzyme levels are often elevated in these cells and this property has been exploited in targeted prodrug-tumor delivery.<sup>30</sup>

Capecitabine (Xeloda) is an orally administered carbamate prodrug of 5-Fluoro-Uracil, requiring a cascade of three enzymes for its bioconversion to the active drug. Capecitabine undergoes intact absorption from the intestine and the final step of bioconversion pathway occurs within the tumors, thus avoiding systemic toxicity.

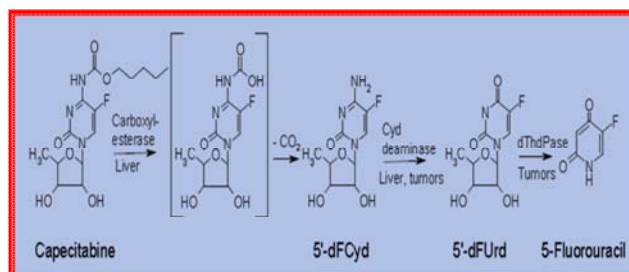


Figure 3: Bioconversion of Capecitabine to 5-Fluorouracil

The enzymatic bioconversion pathway<sup>31</sup> (Figure 3) is initiated in the liver where human carboxyl-esterases 1 and 2 cleave the ester bond of the carbamate, which is followed by a rapid decarboxylation reaction resulting in the formation of 5<sup>1</sup>-deoxy-5- fluorocytidine. The reaction

continues in liver and partly in tumors by cytidine deaminase and forms 5<sup>1</sup>-deoxyuridine. The final activation step occurs in tumors, where thymidine phosphorylase liberates the active drug 5-FluoroUracil. The bioavailability of 5-FU is almost 100 % after the oral administration of Capecitabine.<sup>31</sup>

### Enzyme-Activated Prodrug Therapy

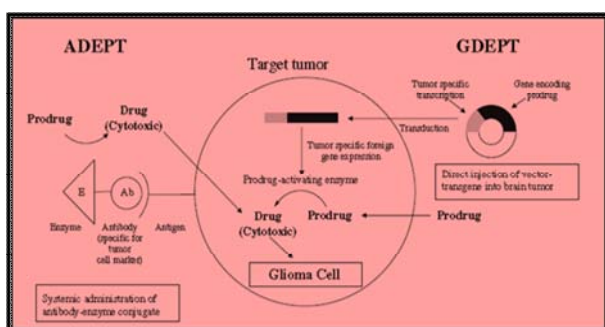
For the treatment of cancer, enzyme-activated prodrug therapy has been used to design specific drug delivery systems. To expand the range of tumors that are susceptible to enzyme-prodrug cancer therapy, prodrug-activating exogenous enzymes can be delivered by using antibodies and genes. First, the drug activating enzyme is targeted and expressed in the tumors and later a non-toxic prodrug that acts as a substrate to enzyme is systemically administered enabling the selective activation of the prodrug in the tumor.<sup>32</sup>

The strategies that have been directed to targeting the tumor are:

- 1) Antibody-directed enzyme prodrug therapy (ADEPT), 2) Gene-directed enzyme prodrug therapy (GDEPT), 3) Viral-directed enzyme prodrug therapy (VDEPT), 4) Macromolecule-directed enzyme prodrug therapy (MDEPT), 5) Lectin-directed enzyme prodrug therapy (LDEPT).

ADEPT and GDEPT are the most common approaches. ADEPT is a two-step therapy, in which the enzyme-antibody conjugate first binds to a tumor-specific antigen on the malignant cell membrane. The inactive prodrug is then administered and activated to an active cytotoxic drug by the localized enzyme. The first clinically tested ADEPT prodrug is 4-[(2-chloroethyl) (2-mesyloxyethyl) amino] benzoyl-L-glutamic acid (CMDA).<sup>33, 34</sup>

The principle of GDEPT is similar, but the enzyme is localized within tumor cells by using a non-viral targeting vector to deliver the gene encoding the enzyme into the tumor cells. The examples of GDEPT include irinotecan, a prodrug of 7-ethyl-10-hydroxy-camptothecin, 5-fluorocytosine, a prodrug of 5-fluorouracil, and cyclophosphamide, a prodrug of 4-hydroxycyclophosphamide.<sup>34, 35</sup>



**Figure 4:** Mechanism of ADEPT and GDEPT

The outline of the mechanisms of ADEPT and GDEPT<sup>36</sup> are illustrated in the (Figure 4)

### Liver- Targeted Drug Delivery

Liver is the most important metabolizing organ and possesses a wide variety of liver-specific metabolic enzymes that are capable of prodrug activation. There are many drug carriers that are capable of targeting drugs to blood vessels of individual tissues, like the antibodies, labeled liposomes, polymers, but they often fail to deliver the drugs to extravascular sites.<sup>37, 38</sup>

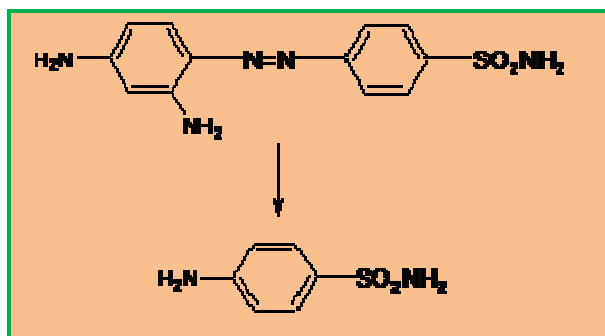
Successful targeting of drugs to liver requires an efficient uptake and conversion of prodrug to the active drug and retaining the drug in the liver for a period of time sufficient for the drug to accumulate to pharmacologically active levels. Usage of HepDirect prodrugs is a new prodrug strategy that is dependent on a CYP-catalyzed cleavage reaction. HepDirect prodrugs are a series of substituted cyclic 1, 3-propanyl esters of phosphates and phosphonates that are designed to undergo a single enzyme-catalyzed oxidative cleavage reaction.

Pradefovir mesylate is a cyclic 1, 3-propanyl ester prodrug of a nucleoside mono-phosphate (NMP), Adefovir (Hepsera), used in the treatment of hepatitis B. Pradefovir undergoes a cytochrome P450 (CYP) 3A4 catalyzed oxidation predominantly in liver hepatocytes. The oxidation results in ring opening and elimination of an aryl vinyl ketone. The released monophosphate adefovir is further converted by nucleotide kinases to the active nucleoside triphosphate (NTP). Pradefovir has demonstrated good efficacy with low systemic adefovir levels, in the clinical trials, which is an indirect evidence for liver targeting.<sup>38-40</sup>

### Colon- Targeted Drug Delivery

Colon-specific delivery system has been effectively used in the treatment of many colonic diseases like irritable bowel syndrome, ulcerative colitis, crohn's disease and colorectal cancer. Currently, the prodrug approach is used to treat the inflammatory bowel diseases (IBD), in which the active drugs are liberated by the action of bacterial enzymes like glucosidases, glucuronidases and azo-reductase in the colon.<sup>41</sup> The prodrugs for colonic delivery undergo low absorption and hydrolysis in the upper part of gastrointestinal tract, enzymatic hydrolysis in the colon, and thereby regenerate the drug from the drug carrier.

Sulfasalazine is an azo prodrug that is metabolised by the intestinal bacteria. Its active moiety, 5-amino-salicylic acid is very effective in treating IBD and was the first bacteria sensitive delivery system. Sulphapyridine acts as the drug carrier. Sulfasalazine undergoes azo reduction in the colon to release 5-amino-salicylic acid and sulphapyridine.<sup>42</sup>



**Figure 5:** Prontosil undergoing reduction to form Sulfanilamide.

Examples of the prodrugs used for colon-targeted drug delivery include Prontosil (Figure 5), Olsalazine, and Budesonide- $\beta$ -D-glucuronides.<sup>43</sup> Some prodrugs and their drug carriers used in targeted drug delivery are illustrated in the TABLE 2.<sup>44</sup>

**Table 2:** Prodrugs and the drug carriers in colon-targeted drug delivery

DRUG INVESTIGATED	DRUG CARRIERS	LINKAGE HYDROLYSED
5-amino-salicylic acid	Azo conjugates Sulphapyridine Glycine	Azo linkage Azo linkage Amide linkage
Dexamethasone	Saccharide carriers	Glycosidic linkage
Salicylic acid	Amino acid conjugates Tyrosine/ Methionine	Amide linkage Amide linkage

## CONCLUSION

Prodrugs definitely will succeed their way in novel drug delivery systems and address the need for precise targeting and efficient delivery of various drugs and therapeutics. The understanding of continued advances in nanotechnology, cellular mechanisms, material science, and engineering will continue to drive innovation in this field. Because of its potential to give the highest efficacy of drugs with minimal adverse effects, site-specific drug delivery i.e., targeting by the prodrugs is one of the biggest goals currently challenging the pharmaceutical and formulation scientists. The future potential of prodrugs is very immense, enabling multimechanistic drug targeting approaches, and it may prove to be the legendary "magic bullet" for delivery of therapeutics. The systems understanding of the delivery scientist combined with the innovative thinking of the medicinal chemist and the cellular understanding of the biologist will conjure up imaginative solutions to therapeutic problems.

## REFERENCES

- Han HK, Amidon GL. Targeted Prodrug Design to Optimize Drug Delivery. *J Pharm Sci* 2 Suppl 1: 2000; 1-11.
- Bhosle D, Bharambe S, Gairola N, Dhaneshwar SS. Mutual Prodrug Concept: Fundamentals and Applications, *Indian J Pharm Sci* 68 Suppl 3: 2006; 286-94.
- Brahmankar DM, Jaiswal SB. *Biopharmaceutics and Pharmacokinetics a Treatise*. New Delhi: Vallabh Prakashan; 1995; 162.
- Sharma PD. *J Sci Ind Res* 45, 1986; 534.
- Robinson JR, Lee VHL. *Controlled Drug Delivery: Fundamentals and Applications*, New York: Marcel Dekker, Inc; 2:1987; 337-69.
- Kim CJ. *Controlled Drug Dosage Form Design*, Florida: CRC Press LLC; 2000; 1-13.
- Albert A. Chemical aspects of selective toxicity, *Nature* 182: 1958; 421-3.
- Harper NJ. Drug Latentiation. *J Med Pharm Chem* 1: 1959; 467-500.
- Harper NJ. Drug Latentiation. *Prog Drug Res* 4: 1962; 221-294
- Stella VJ, Charman WN, Naringrekar VH. Prodrugs. Do they have advantages in clinical practice? *Drugs* 29: 1985; 455-473.
- Sinkula AA, Yalkowsky SH. Rationale for design of biologically reversible drug derivatives: Prodrugs. *J Pharm Sci* 64; 2: 1975; 181-200.
- Higuchi T, Stella V. *Prodrugs as Novel Drug Delivery Systems*. Washington: American Chemical Society; 1975.
- Roche EB. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. Washington: American Pharmaceutical Association; 1977.
- Stella VJ. Prodrugs as therapeutics. *Exp Opin* 14: 2004; 277-280.
- Stella, V.J., Preface. *Adv Drug Deliv Res.*, 19: 1996, 111-114.
- Hirayama F, Uekama K. Cyclodextrin-based controlled drug release system. *Adv Drug Deliv Rev* 36 Suppl 1: 1999; 125-141.
- Stella VJ, Michelson TJ, and Pipkin JD. Prodrugs: The control of drug delivery via bioreversible chemical modification. In: Juliano, R. L, editor. *Drug Delivery Systems: Characteristics and Biomedical Applications*. New York: Oxford University Press; 1980. p. 110–70.
- Ranade VV and Hollinger MA. *Drug Delivery Systems*, 2<sup>nd</sup> ed. Boca Raton, FL: CRC Press; 2004; 290–9.
- Stella VJ. Prodrugs Strategies for Improving DrugLike Properties. In: Borchardt RT, Kerns EH, Hageman MJ, Thakker DR, Stevens JL, editors. *Optimizing the "DrugLike" Properties of Leads in Drug Discovery*. 1st ed. New York: Springer Science + Business Media; 2006. p. 221-237.
- Wu KM. A new classification of Prodrugs: Regulatory Perspectives. *Pharmaceuticals* 2: 2009; 77-81.
- Testa B. Prodrug research: futile or fertile? *Biochem Pharmacol* 68: 2004; 2097-2106.
- Rowland M and McLachlan A. Pharmacokinetic Considerations of Regional Administration and Drug Targeting: Influence of Site of Input in Target Tissue and Flux of Binding Protein. *J Pharmacokinetic Biopharm* 24:1996; 369-87.
- Suzuki H, Nakai D, Takeshi S and Sugiyama Y. Design of a Drug Delivery System for Targeting Based on Pharmacokinetic Considerations. *Adv Drug Deliv Rev* 19:1996; 335-57.



24. Ettmayer P, Amidon GL, Clement B, Testa B. Lessons learned from marketed and investigational prodrugs. *J Med Chem* 47: 2004; 2393-404.
25. Petrak K. Essential properties of drug targeting delivery systems. *Drug Discov Today* 10: 2005; 1667-73.
26. Siegal T, ZylberKatz E. Strategies for increasing drug delivery to the brain: focus on brain lymphoma. *Clin Pharmacokinet* 41:2002; 171-86.
27. De-Boer AG, Gaillard PJ. Drug targeting to the brain. *Annu Rev Pharmacol Toxicol* 47: 2007; 323-55.
28. Anderson BD. Prodrugs for improved CNS delivery. *Adv Drug Del Rev* 19: 1996; 171-202.
29. Alberts B, Bray D, Lewis J, Raff M, Roberts K and Watson J. *Molecular Biology of the Cell*. New York: Garland Science Publishing; 1994.
30. Aisner J. Overview of the changing paradigm in cancer treatment: Oral chemotherapy. *Am J Health Sys Pharm* 64: 2007; 54-7.
31. Walko CM, Lindley C. Capecitabine: a review. *Clin Ther* 27: 2005; 23-44.
32. Hamstra DA and Rehemtulla A. Toward an enzyme/prodrug strategy for cancer gene therapy: Endogenous activation of carboxypeptidase Amutants by PACE/furin family of propeptidases. *Hum Gene Ther* 10: 1999; 235–248.
33. Sharma SK, Bagshawe KD and Begent RH. Advances in antibody-directed enzyme prodrug therapy. *Curr Opin Investig Drugs* 6: 2005; 611-5.
34. Shanbhag A, Yam N and Jasti B. Prodrugs as Drug Delivery Systems. In: Li X, Jasti BR, editors. *Design of Controlled Release Drug Delivery Systems, USA: McGraw-Hill Chemical Engineering*; 2006 p. 75-107.
35. Dachs GU, Tupper J and Tozer GM. From bench to bedside for gene-directed enzyme prodrug therapy of cancer. *Anticancer Drugs* 16 Suppl 4: 2005; 349-59.
36. Rautio J, Laine K, Gynther M and Savolainen J. Prodrug approaches for CNS delivery. *AAPS J* 1: 2008; 92-102.
37. Van Montfoort JE, Hagenbuch B, Groothuis GM, Koepsell H and Meier PJ. Drug uptake systems in liver and kidney. *Curr Drug Metab* 4: 2003; 185-211.
38. Erion MD, Reddy KR, Boyer SH, Matelich MC, Galeno JG, Lemus RH, et al. Design, Synthesis and Characterization of a Series of Cytochrome P450 3A-Activated Prodrugs (HepDirect™ Prodrugs) Useful for Targeting Phosph(on)ate-Based Drugs to the Liver. *J Am Chem Soc* 126:2004a; 5154–63.
39. Erion MD, Bullough DA, Lin CC and Hong Z. HepDirect prodrugs for targeting nucleotide based antiviral drugs to the liver. *Curr Opin Investig Drugs* 7: 2006; 109-17.
40. Erion MD. Prodrugs for Liver-targeted Drug Delivery. In: Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, Tilley JW, editors. *Prodrugs: Challenges and Rewards*. Newyork: AAPS Press/Springer; 1: 2007; 544-67.
41. Hirayama F, Uekama K. Colonic Delivery. In: Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, Tilley JW, editors. *Prodrugs: Challenges and Rewards*. Newyork: AAPS Press/Springer; 1: 2007; 684-99.
42. Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ. Colon Targeted Drug Delivery: Different Approaches. *J Young Pharm* 1: 2009; 13-9.
43. Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, Tilley JW. *Prodrugs: Challenges and Rewards*, Newyork: AAPS Press/Springer; 1: 2007; 5-37.
44. Tiwari G, Tiwari R, Wal P, Wal A, Rai AK. Primary and novel approaches for colon targeted drug delivery- A review. *Int J Drug Del* 1: 2010; 1-11.

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