PRO-DRUG DEVELOPMENTS AND ITS SCOPE-AN OVERVIEW

Abstract

Prodrugs can be reversed into biological aspect and they are in form of inactive drug of parent drugs. When prodrug goes in the body, they convert them into their active form. Prodrug concept is for improving biological and physiochemical properties of drugs for their increased effects. In order to form modern prodrugs, they have some modifications include cellular and molecular parameters to give desired drug effect and target site. Prodrugs concept if useful to deliver new concept and developing new drugs forms. The concept of developing new prodrugs if for enhancement of the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active molecules and so decreasing problems to a drug's improvement and benefits. Most of the prodrugs development is done to permeate drugs through the lipophilic membrane of body and to improve drug water solubility. In drug discovery and development, prodrugs are used mainly for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents.

Keywords: *Prodrugs, Bio pharmaceutics, Drug absorption, Oral administration, Drug targeting.*

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I. INTRODUCTION

Enhanced techniques of modern drug discovery, helps to develop new novel chemical molecules with increased pharmacological efficacy and effects of drugs [1]. These new processes have developed many targets, as many of the new drug molecules have certain unacceptable or unsuitable physicochemical characteristics and they need chemical Changes or use of Process technologies to achieve acceptable performance and pass the drug development process suitably [2]. In oncology process, prodrugs are also used for targeted drug delivery, for reducing side effects and improve the endurance of chemotherapy [3]. Prodrugs are also used for enhancing time period of drugs action and they acts are sustained drug release forms.[4]

II. CONTINUED NEED FOR PRODRUGS

As per drug development needs, prodrug approach is going to take success for showing effective treatment against various diseases and also it is still need to develop prodrugs action with the help of chemical drug designs. For consideration of biological systems and their thermodynamics study have interest in research like receptor site of action of prodrugs and enzymes. In todays worlds various technologies such as quantum mechanics, semi empirical, density functional theory(DET), Molecular Mechanics(MM) are going on increasing order to give pathways for study of prodrugs. Using these technologies, it is need to develop prodrugs in order to increase effectiveness of drug delivery system [5]

III. THE PRODRUG CONCEPT

The prodrug process is shown in below table. The main aim behind prodrug concept is to formulate the drug molecule in the specific form so that the effect of the drug is shown by specific way. The problems such as physiological barriers in drug delivery as specific site or Trans membrane barriers. Prodrug are the chemical entities which are formulate in the inactive form and they showed their effect when they delivered inside the body and then after certain time they starts their effects by activation of drug molecules. [6]There are many pathways in which we an delivered the prodrugs such as transdermal route, oral route, intravenous route, intramuscular route, inhalation route, and many more. The growth of such development of prodrugs and their positive effects inside the body showing more interest in prodrugs concept.[7] other than these routes one more therapy for prodrugs is enzyme prodrug therapy (DEPT) in which enzymes are used for showing the activity of prodrug by enzyme production process. Prodrugs so called as they altered their form after their activation and change their physiochemical properties and that’s why called as bio reversible and now accepted by various groups. [8]

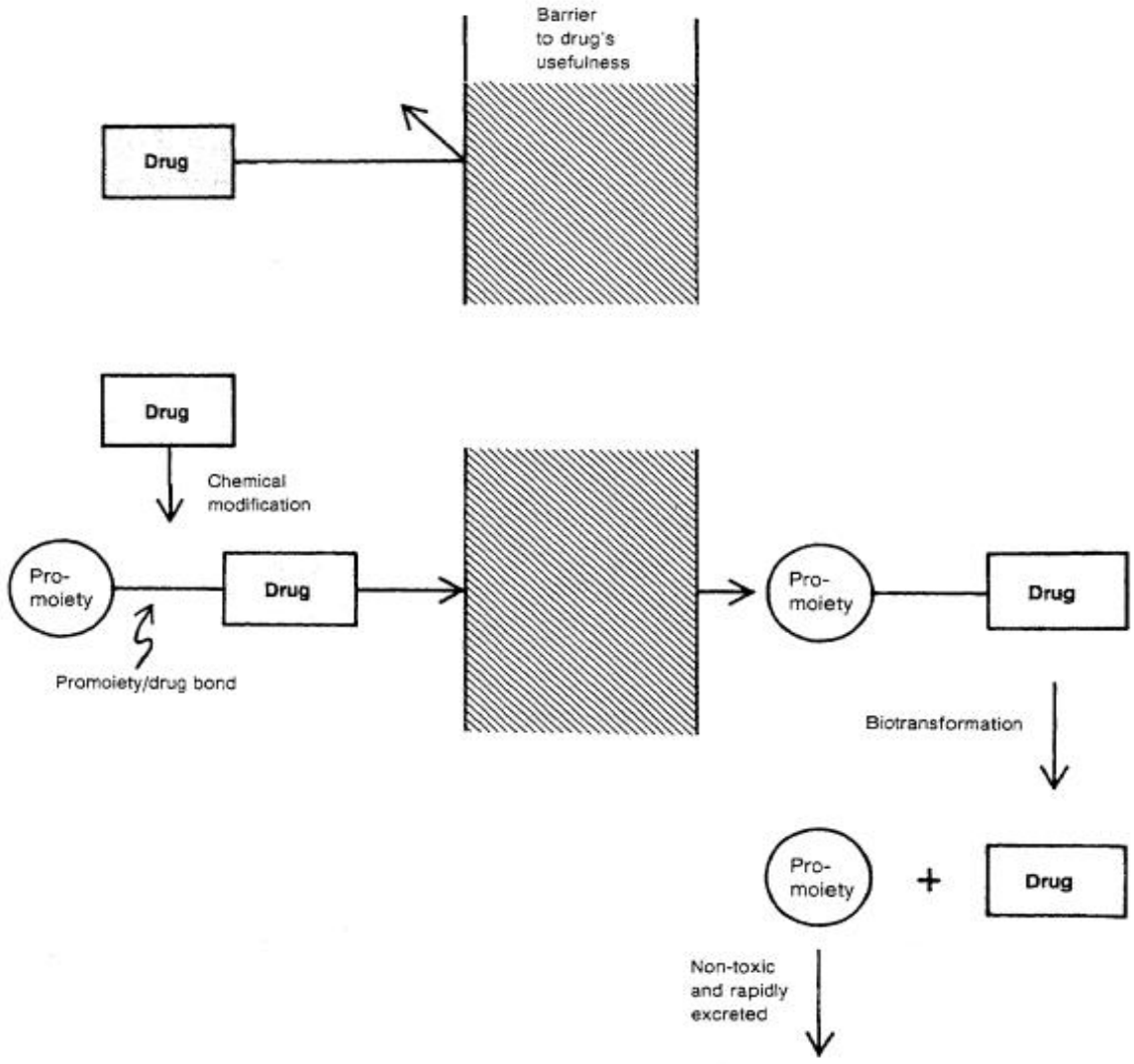
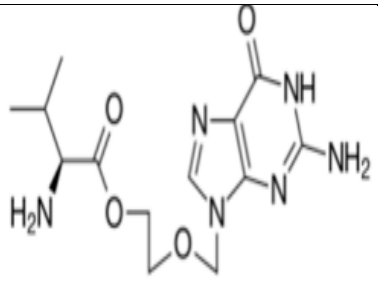
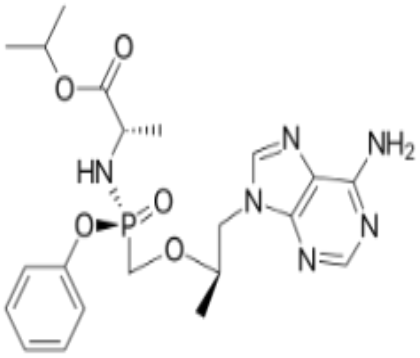
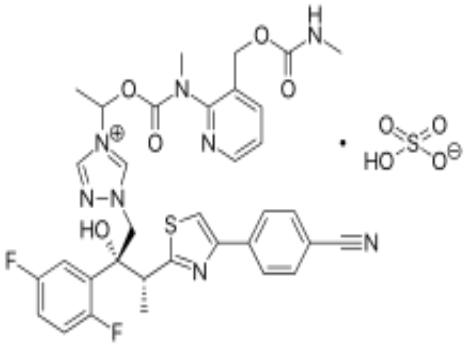
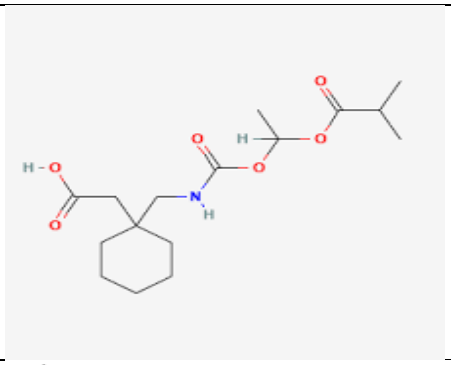
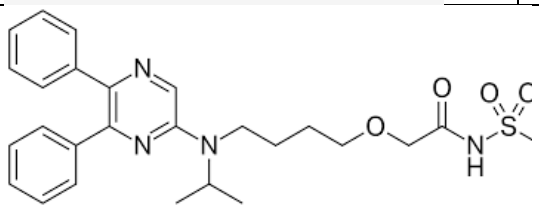
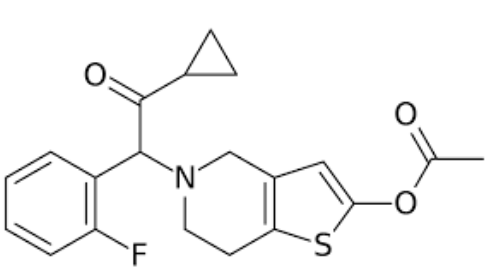


Figure 1: Schematic Representation of the 'Prodrug' Concept [9]

IV. PRODRUG STRUCTURE

Table 1: Prodrug Structures and their Therapeutic Uses [10]

Prodrug	Structure	Therapeutic Uses
Valacyclovir		Herpesvirus

Tenofovir alafenamide		HIV/AIDS and chronic hepatitis B
Isavuconazonium sulfate		Invasive Aspergillosis/Mucormycosis
Gabapentin enacarbil		Restless leg syndrome, postherpetic neuralgia
Selexipag		Pulmonary arterial hypertension
Prasugrel		Prevention of thrombotic and cardiovascular events

V. PRODRUG ACTIVATION

While studying the activation of prodrugs there are certain challenges like whether the drug molecule has to be activated before absorption or after absorption and then will reach to systemic circulation. Certain barriers for activation should be taken into consideration. There are many examples of studying the post and pre absorption of that study [11] The most common of which is making a prodrug susceptible to abundant enzymes by functionalization with a group that can be cleaved to produce the active form of the drug. The conversion of prodrug from its inactive form to its active form, CYP450 required and it is a biological process in liver, GIT tract, Plasma and other receptors. The most common can be used that while formulation of prodrugs the chemical conversion f inactive form into its active form is done by using enzymes functionalization and can be made easy for action [12, 13]

VI. CLINICAL PRODRUGS FOR ORAL DRUG DELIVERY

Active drug moieties are converted into their inactive form and they called as prodrugs. And they undergo conversion in the body by releasing active parent drug from the inactive form. The invention of prodrug concept is for overcoming of certain factors like pharmaceutical factors, Pharmacokinetic factors and pharmacodynamics factors. And these factors are responsible for problems such as low oral absorption, poor stability of drugs, not target delivery and permeability of drug molecules through the transmembrane. Over 10% of the drugs in form of prodrugs available in market. In between 2000 and 2008, over 20% medicines in prodrugs form approved. [13] If we take example of increased bioavailability and increased permeability and drug targeting, some of approved antiviral drugs example we can give such as- tenofovir and sofosbuvir. These both drugs are developed using technology of Protide. This technology depends on the process of nucleotide analog delivers to the tissues and cells. The process is that it masks the monophosphate hydroxyl groups by aromatic group of ester amino acids. [14]. In order to increase the absorption of drugs in the oral drug absorption and administration. This is followed the traditional drugs approach. This can be done by reducing the effect of charged molecules and increasing lipophilicity and diffusion by various esters of COOH including hydrolysis [15]

VII. BARRIERS TO DRUG DEVELOPMENT

While developing a new products like prodrugs there is always have chances of barriers and it is impossible to overcome barriers every time and that’s why these problems can be reduced when drugs in in the form of drugs. Researchers like Aliens and Simonis in 1974 introduced the process of development of drugs which includes three phases like- one is pharmaceutical, second one pharmacokinetic and last one pharmacodynamics phase. 1) Pharmacokinetic phase includes which the drug gives effects on the body and pharmacokinetic phase shows that how body reacts on the drugs like absorption, metabolism, distribution and excretion [10, 16]. 2) Pharmaceutical phase is for formulation of the drug products. Its starts from finding the drugs for formulation including its identification of new molecules with its effects on drug delivery system. In human body there are various delivery system like oral drug delivery system, Transdermal drug delivery system, Patch delivery system, buccal drug delivery system and all these includes tablets, capsules, patches, ointments, cream, etc.

There are mainly 2 barriers which seen while delivery of commercial drugs:

- Aesthetic properties of that drug molecule which can directly or indirectly affect drug action, e.g., odour, taste, pain while taking drugs, GIT irritation
- Development problems may be like instability of those drugs, its physiochemical properties, dosage form suitability [17].

VIII. USE OF PRODRUGS TO OVERCOME PHARMACEUTICAL BARRIERS

The stability of drugs is very important aspect while formulation. The chemical molecule having its therapeutic activity is required for showing action in body. But it is always target that the effect should be given when the drugs have stability. The taste and odour should not change with time and the drugs which are delivered in the body should not show gastric irritation when administered. If we consider intravenous route for administration of drugs molecules, the drug should have proper solubility and remain in those forms for its specific time while delivering drugs action [18].

Certain pathways in which there is alteration in the properties of prodrugs like its physiochemical properties that's why they used in form of prodrug to control its effects
These changes can be given as:

- Rate of absorption
- The rate at which the inactive form of drug converts into its active form
  3) Rate at which the drug bind to certain tissue or enzyme
- Rate of distribution after binding of drug molecules to the receptor carriers. [19]

IX. CONCLUSIONS

The prodrug delivery in the human body is now taking success as some of the drugs are unable to remain stable in their active form and for them prodrug concept is best. It can be assured that the future has large scope for prodrug concept and its development by using process like pro drug activation and make easy delivery of drugs

REFERENCES

[1] Lipinski C.A., Lombardo F., Dominy B.W., Feeney P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv Rev. 2001; 46: 3–26.
[2] .Knittel J.J., Zavod R.M. Drug design and relationship of functional groups to pharmacologic activity. In: Lemke T., Williams D.A., Roche V.F., Zito S.W., editors. Foye's Principles of Medicinal Chemistry. 7th ed. Wolters Kluwer Lippincott Williams and Wilkins; London, UK: 2013. p.51.
[3] Najjar A, Rajabi N, Karaman R. Recent approaches to platinum(iv) prodrugs: a variety of strategies for enhanced delivery and efficacy. Curr Pharm Des. 2017;23(16):2366–2376.
[4] Brams M, Mao AR, Doyle RL. Onset of efficacy of long-acting psychostimulants in pediatric attention-deficit/hyperactivity disorder. Postgrad Med. 2008 Sep;120(3):69–88.
[5] 10. Karaman R. Prodrugs design: a new era. New York, USA: Nova Science Publishers, Incorporated; 2014.
[6] Davies, G.E.; Driver, G.W.; Hoggarth, E.; Martin, A.R.; Paige, M.F.C.; Rose, F.L. and Wilson, B.R.: Studies in the chemotherapy of tuberculosis: Ethyl mercaptan and related compounds. British Journal of Pharmacology 11: 351-356 (1956)
[7] Yang Y.-h., Aloysius H., Inoyama D., Chen Y., Hu L.-q. Enzyme-mediated hydrolytic activation of

prodrugs. Acta Pharm. Sin. B. 2011;1:143–159.
[8] Ho, N.F.H.; Park, J.Y.; Morozowich, W. and Higuchi, W.L: Physical model approach to the design of drugs with improved intestinal absorption; in Roche (Ed.) Design of Biopharmaceutical Properties through Prodrugs and Analogs, pp. 136-227 (American Pharmaceutical Association, Washington, DC 1977).
[9] VJ. Stella, W.N A. Charman and V.H. Naringrekar, Prodrugs Do They Have Advantages in Clinical Practice? Drugs 29: 455-473 (1985)
[10] Milica Markovic † , Shimon Ben-Shabat and Arik Dahan, Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products, Pharmaceutics 2020, 12, 1031
[11] Sun J., Dahan A., Amidon G.L. Enhancing the intestinal absorption of molecules containing the polar guanidino functionality: A double-targeted prodrug approach. J. Med. Chem. 2010;53:624–632.
[12] Karaman R. Prodrugs design: a new era. New York, USA: Nova Science Publishers, Incorporated; 2014.
[13] Alanazi A.S., James E., Mehellou Y. The protide prodrug technology: Where next? ACS Med. Chem. Lett. 2019;10:2–5.
[14] Bildstein L., Dubernet C., Couvreur P. Prodrug-based intracellular delivery of anticancer agents. Adv. Drug Deliv. Rev. 2011;63:3–23.
[15] Beaumont K., Webster R., Gardner I., Dack K. Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: Challenges to the discovery scientist. Curr. Drug Metab. 2003;4:461–485.
[16] Ariens, E.J.: Molecular pharmacology, a basis for drug design; in Jucker (Ed.) Progress in Drug Research, Vol. 10, pp. 429-529 (Birkhauser Verlag, Basel 1966)
[17] Roche, E.B. (Ed.): Design of Biopharmaceutical Properties through Prodrugs and Analogs (American Pharmaceutical Association, Washington, DC 1977a).
[18] Bodor, N.: Novel approaches in prodrug design; in Bundgaard et al. Optimization of Drug Delivery, pp. 156-177 (Munksgaard, Copenhagen 1982).
[19] Ho, N.F.H.; Park, J.Y.; Morozowich, W. and Higuchi, W.L: Physical model approach to the design of drugs with improved intestinal absorption; in Roche (Ed.) Design of Biopharmaceutical Properties through Prodrugs and Analogs, pp. 136-227 (American Pharmaceutical Association, Washington, DC 1977)

