PRODRUG BASED NANOPARTICLE THERAPEUTICS: CHALLENGES AND FUTURE PROSPECTS

Abstract

Prodrug was introduced to overcome certain problems in the drugs which consequently led the scientists to switch from the traditional methods in producing classical prodrugs to designing and invoking prodrugs. In the coming years, prodrug-based nanoparticles will be a focus for the researchers to develop drugs to cure chronic illness as it improves efficacy and lessens side effects. The current review paper tries to focus on the benefits, challenges and the future prospects of prodrug-based nanoparticles.

Keywords: Prodrug; nanoparticle; chronic illness; cancer; prodrug-based nanoparticle; drug delivery

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I. INTRODUCTION

Prodrugs are particles which are pharmacologically inactive but when introduced inside a host they become active due to enzymatic actions [1-3]. It is basically a drug coated with a safe moiety to make it inactive due to various properties of the drug which after intake becomes dissolved as depicted in Figure 1. The prodrug approach was developed to eliminate some undesirable physicochemical, biological and organoleptic properties of some existing drugs. Some prodrugs are linked with two moieties instead of one and such prodrugs are called "Codrugs" or "Mutual prodrugs". A few examples of codrugs are sulfasalazine, mesalazine, latanoprostene bunod, etc. Over the past few decades, it has experienced tremendous success and is now regarded as a promising and well-established method for the creation of new entities with superior efficacy, selectivity, decreased toxicity and increased bioavailability [4].

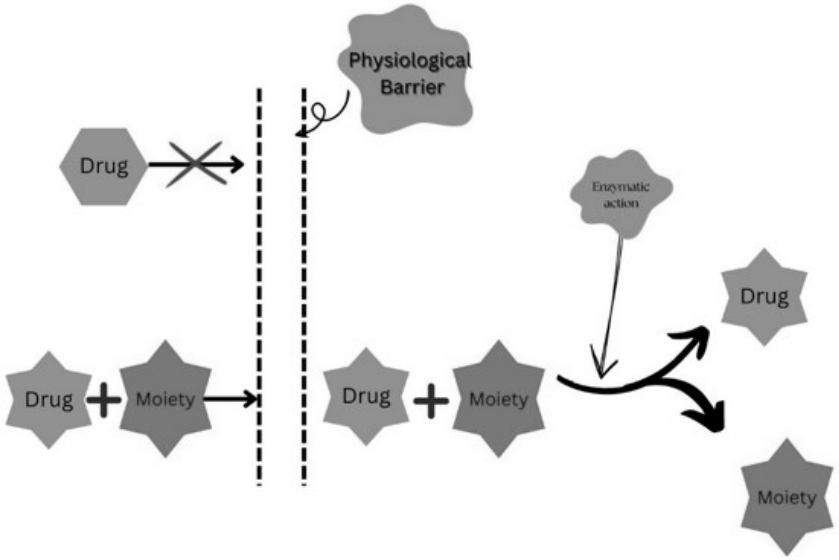

Figure 1: Schematic representation showing the concept of Prodrug.

Prodrug uses various tactics to optimize pharmacokinetics (drug delivery) and physicochemical properties to decrease toxicity and to aim specific tissues or cells. In order to make a prodrug more approachable, it is made susceptible to various enzymes by functionalization with a group that can be cleaved to produce active form [5]. Prodrug have various benefits that helps in cellular uptake, precursors in biological conversion pathways, increase duration of action of medicines, improves pharmacokinetic properties, etc.

Prodrug-based nanoparticle is the encapsulation of therapeutics within nanocarriers that helps in improving the kinetics as well as therapeutic efficacy of the drug. Although challenging, it has potential in the near future to overcome issues related to oncology and other therapeutic areas. The development of nanotechnology has had a substantial influence on medication delivery during the past ten years, where it focuses on developing nanoscale particles in order to improve the medication delivery [6-8]. In this chapter we will be focussing on prodrug-based nanoparticulate drug delivery strategy in combination with cancer therapy as prodrug-mediated and nanomedicine-mediated treatments stand at the forefront of cancer management these days. In view of the fast development of anti-cancer strategy, this chapter focuses on the most recent advances of prodrug-based nanoparticle drug

delivery systems for anti-cancer therapies resulting in enhanced chemotherapeutic efficiency, overcoming the multi drug resistance (MDR) and hindering metastasis.

Cancer is a complex disease in which some of the body's cells grow uncontrollably and spread to other parts of the body [3]. Cancer is also one of the principal causes of death in developed countries as both the incidence and mortality of cancers are rising unceasingly. Even though a hefty amount of compelling chemotherapeutical anticancer agents has been used successfully in clinical rehearsal, no significant improvement has been seen in cancer treatment. This is due to the absence of selectivity against cancer cells as well as the toxic side effects associated with the drug [9]. Nanomedicine is well-defined as the therapeutic application of nanotechnology, denoting a multi-disciplinary field of nanotechnology, medicine, chemistry and material science. Though emerged recently, this field has exhibited dynamic vitality associating the hasty development of nanotechnology. A broad range of nanomedicines has been developed for various medical applications, especially for anti-cancers; cancer being one of the lethal killers to human beings [10].

In the war against cancer, there has been three major concerns leading to high rate of mortality and reappearance: the severe toxic side effect of anti-cancer drugs to normal tissues due to the absence of tumour-selectivity; the multi-drug resistance to free chemotherapeutic drugs and the deadly metastases of cancer cells. The advancement of state-of-art prodrug-based nanoparticle drug delivery systems (PNDDS) is anticipated to overcome these obstacles. A distinctive characteristic of prodrug-based nanomedicines is that they need to be activated by a stimulus or multi-stimulus to produce an anti-tumour effect. A better understanding of various responsive approaches could aid researchers in perceiving the mechanism of prodrug-based nanomedicines efficiently and further improve their design strategy. In addition, the current development and future challenges of prodrug-based nanomedicines has been discussed which could help readers to understand the structure and development of prodrug-based cancer nanomedicines to design rational and effective drugs for clinical use.

II. BENEFITS OF PRODRUG

The prodrug strategy can be tailor made by fine-tuning the chemical properties of a compound, one can accomplish a diversity of properties including aiding the process of formulation, optimizing bioavailability as well as developing innovative intellectual property. Products promoted nowadays are typically envisioned to have the following advantages as (a) Improved formulation properties which aids to mask functional groups, enable formulation of nanoparticle, control solubility and modify steric properties; (b) customizable pharmacokinetic (PK) properties which aids to customize the route of administration, improve bioavailability, tune absorption profiles, increase membrane permeability, tailor uptake of cell, control binding of protein, allow blood-brain-barrier permeation as well as refine distribution, excretion and half-life; (c) optimizable pharmodynamics (PD) effects include optimizing metabolic stability, prevent metabolic activation, permit intracellular conversion as well as embrace bacteria-labile linker chemistry; (d) toxicity reduction by minimizing side-effects, controlling the release of cytokine, avoiding interactions with off-target receptor, improving liver metabolism; and (e) rationalizing the process of development by providing simplified regulatory pathway, reduction in development costs, extending intellectual property coverage and enhanced stability [11, 12]. A schematic diagram has been presented in Figure 2, to show the advantages of nanoparticle-based prodrug.

Figure 3 shows different classes of nanocarriers which can be classified into three groups viz. Inorganic, Polymeric and Lipid based which are further subclassified into various types. Inorganic nanocarriers are subclassified as quantum dot, gold nanoparticles, silica nanoparticles, magnetic nanoparticles, carbon nanoparticles, etc. Polymeric nanocarriers are classified as polymeric micelles, dendrimers, polymeric hydrogels, polymeric drug conjugates, etc. Lipid based nanocarriers are classified as liposomes, solid- lipid nanoparticles, phospholipid micelles, nanoemulsions and self-emulsifying drug delivery system [15]

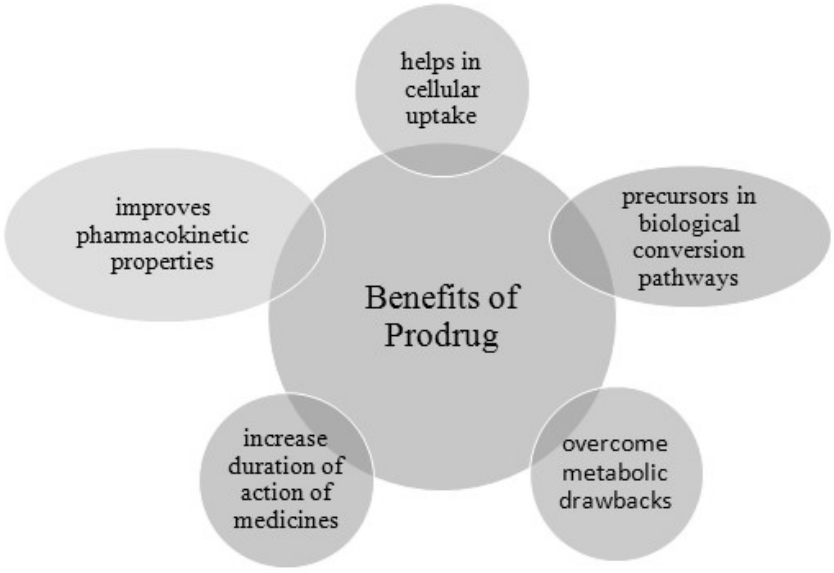

Figure 2: Schematic diagram depicting various benefits of using prodrug.

III. CANCER TREATMENT

The field of nanomedicines have progressed tremendously, leading to emergence of new drugs as a result of rapid development of nanotechnology. In contrast, the effective delivery of drugs to tumour sites still remains a great challenge. Prodrug-based cancer nanomedicines thus developed owing to their exclusive advantages including reduced side effects, efficient targeting, high drug load efficiency and real-time controllability [13]. Cisplatin is one of the oldest and structurally simple anticancer drugs. Upon intake it loses the chlorine which makes the platinum reactive and capable of creating two more bonds which can further be helpful in lessening its toxicity and produce platinum-based prodrugs. Two of the examples are satraplatin and iproplatin. Squalene, is an isoprenoid which is naturally found. It helps in producing polymeric nanoparticles to fight against cancer.

IV. CHALLENGES

To act as a prodrug there are certain ideal properties like appropriate aqueous solubility, stability to reach target site in the host, passive permeability, effective conversion, minimal non-productive pathways, a safe profile to avoid inhibition of drug-metabolizing enzymes, better targeting-fewer side effects, etc. Hence it is difficult and challenging to get all these criteria in one prodrug. One needs to concentrate on these different properties. Despite the benefits that nanoparticle technology can provide, the rate of clinical translation

that is effective is still modest [14]. It also faces problems like unfavorable loading and leakage. The few challenges that are faced to develop a new prodrug are listed in Figure 4.

The study by Karaman reported that the widely used chemotherapeutic agent cisplatin and other approved platinum (II) agents have failed despite numerous attempts [11]. At different clinical trials the development of Ormaplatin (Tetraplatin, NSC 363812), a platinum (IV) complex, Iproplatin, a platinum (IV) complex structurally similar to ormaplatin and Satraplatin, a platinum-based antineoplastic agent was halted due to unpredictable neurotoxicity, failure to show activity, unfavorable PK and premature reduction to the active compound respectively [15-17]. In order to increase efficacy and to reduce side effects, nanoparticle-based drug delivery systems have the ability to change the PK properties of their APIs, which may include a longer half-life and higher distribution to the site of action. Sometimes a significant portion of the drug that has been adsorbed is swiftly released after injection that may result in severe toxicity.

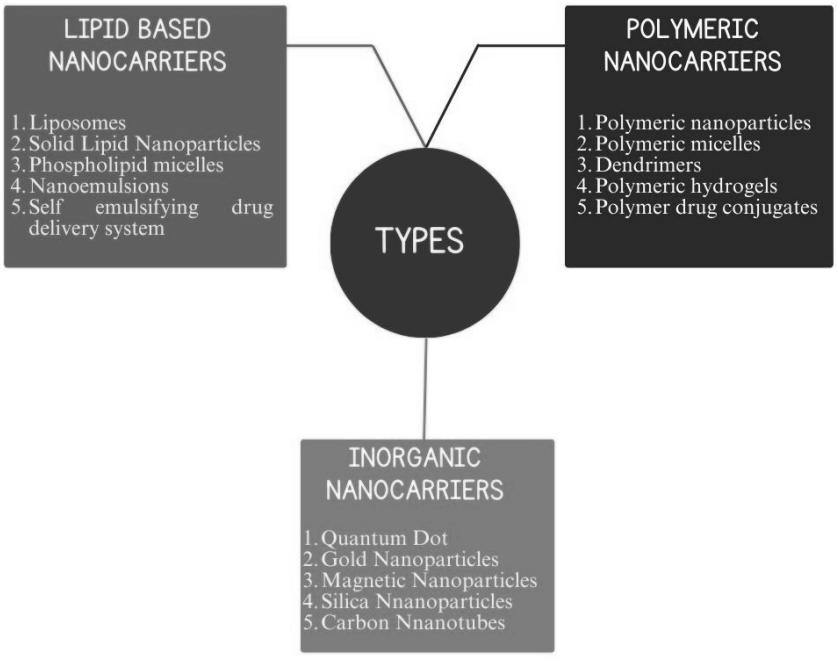

Figure 3: Classification of groups of Nanoparticles based Drug delivery system.

With advancement in the use of prodrug-based nanoparticles in providing effective medications for various diseases; it further requires the crucial use of computational techniques such as ab initio, Density Functional Theory, semi-empirical and molecular mechanics approaches, as well as X-ray and spectroscopic data on enzymes and transporters, to produce drugs with high bioavailability. Moreover, the use of lipid instead of ester as bio responsive linker will be challenging. Safety measures has to be taken to avoid changes in both physical and biochemical properties of the prodrug while keeping in mind of absorption, distribution metabolism, excretion and toxicity (ADMET) properties.

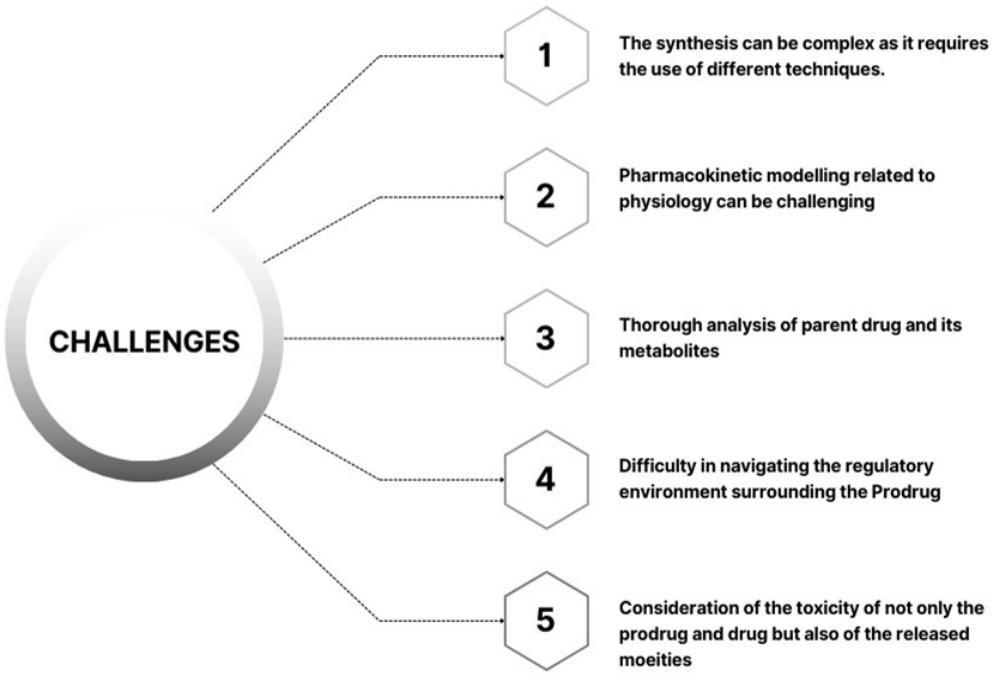

Figure 4: Mind map showing certain challenges to develop prodrug.

V. FUTURE PROSPECTS

To enhance nanomedicine and find novel treatments, prodrug-based nanoparticle drug delivery systems (PNDDS) have been investigated [18]. The prodrug strategy has shown to be extremely effective over the previous few years. They were traditionally prepared as a strategy to solve problems of poor clinical outcomes like presence of certain functional groups that leads to toxicity or inappropriate bioavailability etc. More recently, they are used as an agent to enhance the use of drugs in clinic and has great scope to play an important role in anticancer therapy [19]. Clinical studies are presently being conducted on nanotechnologies that were first described a decade ago utilising conventional linkers like esters and hydrazones.

In past few years, there is a rapid surge in bio-responsive systems, three most frequently employed strategies in nanotherapy includes antibody-drug conjugates, gene-directed enzyme prodrug treatment and gene-directed enzyme prodrug therapy. It has also been seen that; earlier prodrug was designed as a last option. But now with the use of new technologies like computational biology, which has given a different approach such as production and layout of linkers. From various studies, prodrugs like Aldoxorubicin, Baloxavirmarboxil, Evofosfamide, Fostemsavir, Pomaglutadmethionil, etc, are thought to have future with the therapeutics [20]. Some of the prodrugs with the future prospects are listed in table 1.

Table 1: Prodrugs with future prospects

Sl. No.	Name of the prodrug	Therapeutic for	References
1.	Aldoxorubicin	Sarcoma	[21]
2.	Baloxavirmarboxil	Influenza Type A and B	[20]
3.	Evofosfamide	Pancreatic Cancer	[22]
4.	Fostemsavir	HIV- 1	[23]
5.	Pomaglumetadmethionil	Schizophrenia	[24]
6.	Romidepsin	Peripheral T-cell lymphoma	[25]
7.	Sofosbuvir	Hepatitis C	[26]
8.	Pretomanid	Tuberculosis	[27]
9.	Tafenoquine	Malaria	[28]
10.	Ceftaroline Fosamil	Bacterial skin infection	[29]
11.	Fosnetupitant	Acute nausea	[30]
12.	Selexipagaa	Pulmonary arterial hypertension	[31]

An analogue to doxorubicin is aldoxorubicin, which can be considered as a therapeutic for Sarconoma. When compared to doxorubicin, aldoxorubicin has been shown to be safer in many ways, such as better pharmacokinetic property and lower toxicity profile. Evofosfamide is also considered as a novel drug against pancreatic cancer because of its activity. It remains inactive in other circumstances but becomes active only under hypoxic condition which is a characteristic of pancreatic cancer [20]. Clinical implementation of several of the techniques like gene therapy and drug conjugates, which are still in the preclinical stage holds a promising future in treating Osteosarcoma [32].

Prodrugs are thus thought to make up about 10% of all commercially available drugs including both small molecular weight and large molecular weight, which has scope to grow further. The National Nanotechnology Initiative (NNI) was also created by National Commission of Science and Technology (NSTC) in 2000 to solve issues faced by the clinicians as well as researchers so that there is a common point in improving the nanomedicines. This project has been found useful and will be beneficial in future too, for the exploration and development of prodrug-based nanomedicines by considering opinions from both researchers and clinical experts.

VI. CONCLUSION

Prodrug modifications may now be used to get drug-like qualities, speeding up the process of obtaining clinical proof of concept. This is due to the greater understanding that a molecule can be engineered with drug-like features at an early stage. It will be easier if reaction mechanism is found out. Although there are some challenges, but if researchers explore more and take advantage of computational drug discovery and design; then it would lead to a larger nanoparticle-based prodrug therapeutic market in the near future. In the field of cancer therapy, it can play a very important role as the number of patients dying has been rapidly increasing specially with late-stage cancer where chemotherapy becomes toxic [34-

35]. This is due to the less specificity of the drugs to select tumorous cells and target normal cells. But with prodrug-based nanoparticles therapeutics, the target can become more specific. It will further help to cure certain other chronic diseases such as Alzheimer's disease, asthma, diabetes, etc. and would also be able to address the problems with conventional medicine.

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