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Review

Recent approaches for reducing hemolytic activity of chemotherapeutic agents

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ABSTRACT

Drug induced hemolysis is a frequent complication associated with chemotherapy. It results from interaction of drug with erythrocyte membrane and leads to cell lysis. In recent past, various approaches were made to reduce drug-induced hemolysis, which includes drug polymer conjugation, drug delivery via colloidal carriers and hydrogels, co-administration of botanical agents and modification in molecular chemistry of drug molecules. The basic concept behind these strategies is to protect the red blood cells from membrane damaging effects of drugs. There are several examples of drug polymer conjugate that either are approved by Food and Drug Administration or are under clinical trial for delivering drugs with reduced toxicities. Likewise, colloidal carriers are also used successfully nowadays for the delivery of various chemotherapeutic agents like gemcitabine and amphotericin B with remarkable decrease in their hemolytic activity. Similarly, co-administration of botanical agents with drugs works as secondary system proving protection and strength to erythrocyte membranes. In addition to the above statement, interaction hindrance between RBC and drug molecule by molecular modification plays an important role in reducing hemolysis. This review predominantly describes the above recent approaches explored to achieve the reduced hemolytic activity of drugs especially chemotherapeutic agents.

Contents

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1. Introduction

Hemolysis is a term used to indicate the breakdown of erythrocyte membrane with release of hemoglobin into the plasma. There are several causes of hemolysis including immunologic abnormalities, antigen–antibody reactions, mechanical injury, certain infections, hereditary and acquired cell membrane disorders, G6PD[1] deficiency, hemoglobinopathies (e.g., sickle cell diseases, thalassemia) and chemotherapeutic agents [1,2]. Hemolysis results in anemia and is a most significant drawback for chemotherapeutic bioactives, limiting their direct use in combating the microbial attack. Most of the chemotherapeutic bioactives viz., carboplatin, cisplatin and nonplatinum prescribed for treating different cancers, have side effects that cause myelosuppression, resulting in severe hemolytic anemia [3]. Myelosuppression is a situation in which there is a decrease in the capacity of the bone marrow to produce blood cells. Primary indications include abnormal paleness of the skin, jaundice, or yellowish texture of skin, eyes, and mouth, high fever, weakness, enlargement of the spleen and liver, tachycardia and heart murmur. Damaged stem cells cause reduction in the WBC[2], platelet, and RBC[3] counts. These in turn, cause vulnerability to infections and excessive bleeding thereof. However, the overall incidence of hemolytic anemia is limited and the chemotherapeutic agent induced hemolysis is likely boundless. Major clinical complication attributable to hemolytic effect is intravenous infusion at higher dose. As a result, practicing clinicians and healthcare administrators face many challenges in treating patients with chemotherapy-induced hemolytic anemia.

The main motivation behind focusing on this topic is that researchers, with the focus on improving the quality of life for patients on chemotherapy have until now somehow overlooked the hemolytic effects and paid attention only to pain and loss of appetite. Intense anemia can lead to predisposition of heart, cardiovascular and lung diseases. Considering the significance, researchers have come up with novel techniques to prevent the undesired hemolytic effect of chemotherapeutic agents among them some of them are patented. A short summary of some of the important patents pertaining to the strategies for reduction of hemolysis is indicated in Table 1. Although, hemolysis is not a restricted effect of chemotherapeutic agents as discussed in the forthcoming section but limiting our search, this review mainly garners some of the recent feasible conceptualizations for reducing the hemolytic activity of chemotherapeutic agents.

1.1. Mechanism of hemolysis

Although, the mechanism of hemolysis is unclear, various attempts have been made to elucidate the mechanism. In general, after administration through intravenous route blood components quickly coat the drug molecules [4]. This enables the RES[4] to recognize the injected molecules. Macrophages also play a significant role in detection of particles/molecules in the blood. As discussed by several researchers the size of nanoparticles greatly influences the clearance by RES. Bigger particles are easily cleared as compared to smaller ones of 150–300 nm size range, leading to the distinct changes in biodistribution properties [5,6]. Conversely, smaller particle avoid RES elimination as reported by Gref et al. [7].

Regarding amphiphilic compounds (chemical compounds containing both hydrophilic and hydrophobic properties), as observed the mechanism of hemolysis involves surfactant membrane interaction and membrane solubilization. Surfactant membrane interaction and membrane disruption may be the root cause of occurrence of hemolysis. Micelle formation also plays a significant role at this step. The molecular events generally take place in five distinct steps, (1) the cell surface absorbs drug/surfactant particles, (2) drug/surfactant gets inserted into the membrane, (3) the changes in arrangement of membrane begin, (4) permeability of membrane increases and (5) finally leads to lysis of membrane (Fig. 1) [8]. The required quantity of surfactant to solubilize a membrane increases with the beginning of formation of micelles. Critical micellar concentration correlates with the above statement [9]. As already, discussed emulsifiers or soaps lead to hemolysis by lowering the interfacial tension of bimolecular lipid film of erythrocytes. While non-polar part of detergent dissolves in oil phase, polar part remains in aqueous medium. As a result, lipid portion of cell membrane is pulled towards aqueous phase, which brings about lysis of cell.

In a study, it has been manifested that the addition of an emulsifier with a high cloud point (phospholipids or non-ionic surfactant) like Synperonic® F-68(HLB approx. 29) resulted in an increase cloud point of the emulsifier mixture leading to higher resistance of the emulsifier film against breakdown. This leads to the formation of an extra layer covering the emulsifier mixed film. This further reduces the direct contact of emulsifier and cell membrane resulting into the reduced incidence of hemolysis. This can be a useful approach for parenteral application [10].

Osmotic swelling is another mechanism of hemolysis induced by drugs that enhance the permeability for small ions, which allows the erythrocyte swelling by water influx to balance the osmotic pressure of the cell. It results in physical rupture of RBCs and hemolysis [11].

Some therapeutic agents like saponins show limited therapeutic application due to hemolytic activity associated with them. The mechanism of action involves the interaction of saponins with lipid membrane of erythrocyte and results in the formation of pores in cell by forming insoluble complex with lipid; in addition, saponins interact with aquaporin and induce hemolysis by intake of water [12].

2. Recent avenues for reducing the hemolytic activity

2.1. Drug polymer conjugation

The concept of drug–polymer conjugation is mostly exploited to enhance the bioavailability and aqueous solubility of less soluble drugs. Simultaneously, this also reveals the ability of drug to deliver in a precise manner [13]. For regulatory purposes, it is defined as New Chemical Entity. Marketed polymer–drug conjugates like Xyotax™ (PGA–paclitaxel), and Oncaspars® demonstrate the potentials of the technology. Polymeric drug conjugates technically consists of a drug, spacer and a polymeric backbone with targeting moiety. Some of the most popular polymers include polyethylene glycol (PEG), N-(2-hydroxypropyl)-methacrylamide copolymers, pullulan, PGA, and poly(L-lysine).

2.1.1. PEGylation

PEGylation is a process where polymer chains of polyethylene glycol are covalently attached to another molecule, normally a drug or any other bioactive moiety. PEGs[5] are synthetic polymers, which are water insoluble and non-ionic. They have the inherent capacity as drug carriers because of their biocompatibility and heterogeneity. PEG is safe polymer with diminutive toxicity, and is normally removed from the body in intact form either by the kidneys or in the feces [14]. It has pronounced effects on biodistribution and pharmacokinetic by increasing blood circulation half-life, reducing the tissue distribution (RES and macrophage uptake). PEGylation is achieved through chemical procedures and enzymatic/genetic processes. Chemical procedure involves two basic steps where the primary step deals with derivatization and activation of PEG with linkers and the second step deals with the subsequent conjugation of these activated PEG moieties with bioactive.

[1] Glucose-6-phosphate dehydrogenase.
[2] White blood cells.
[3] Red blood cells.
[4] Reticuloendothelial system.
[5] Polyethylene glycol.