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Development and optimization of paclitaxel loaded Eudragit/PLGA nanoparticles by simplex lattice mixture design: Exploration of improved hemocompatibility and *in vivo* kinetics

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ABSTRACT

Anemia is the most common hematological abnormality of chemotherapy, which is responsible for poor clinical outcomes. To overcome this complication, the present study was aimed for developing a Eudragit/polylactic-co-glycolic acid (PLGA) based nanoparticulate system for a model drug paclitaxel (PTX). The study was planned using a simplex lattice mixture design. PTX nanoparticles (PTXNp) were evaluated *in vitro* for physicochemical properties, hemolytic effects and cytotoxic effects. Further, the nanoparticles were subjected to *in vivo* screening using rats for hemocompatibility, pharmacokinetic profile, and biodistribution to the vital organs. The PTXNps were 65.77–214.73 nm in size, showed more than 60% sustained drug release in 360 h and caused less than 8% hemolysis. The parameters like red blood cell count, activated partial thromboplastin time (aPTT), prothrombin time (PT) and C3 complement were similar to the negative control. Cytotoxicity results suggested that all the PTXNp demonstrated drug concentration-dependent cytotoxicity. The *in vivo* pharmacokinetic study concluded that PTXNp formulations had significantly higher blood AUC (93.194.55–163,071.15 h*ng/mL), longer half-lives (5.80–6.35 h) and extended mean residence times (6.05–8.54 h) in comparison to PTX solution ($p < 0.05$). Overall, the study provides a nanoparticulate drug delivery system to deliver PTX safely and effectively along with reducing the associated hematological adverse effects.

1. Introduction

Breast cancer is one of the most common cancers in women. According to the Global Cancer Observatory and the International Agency for Research on Cancer (IARC), about 2.26 million new breast cancer cases (11.7% of all new cancer cases) were registered in 2020, and about 6.8 million deaths (6.9% of all deaths due to cancer) were reported due to breast cancer in 2020. Further, it is projected that the number of cases will rise from 2.26 to 2.96 million by 2040 [1].

Currently, chemotherapy is the most utilized treatment for breast cancer. However, it leads to several clinical adverse effects. These adverse effects can range from but are not limited to hair loss, fatigue,

Abbreviations: AUC, area under curve in ng hr/mL; C_0, initial concentration; Cl, Clearance; C_{last}, concentration corresponding to time of last measurable observed concentration; C_{max}, maximum observed concentration occurring at time T_{max}; DLS, dynamic light scattering; EPR, enhanced permeation and retention; FDA, Food and Drug Administration; Hb, Hemoglobin; HCT, haematocrit percentage; IARC, International Agency for Research on Cancer; MCH, mean corpuscular Hb, and MCHC, mean corpuscular Hb concentration; MCV, mean corpuscular volume; PBS, phosphate buffered saline; PLGA, polylactic-co-glycolic acid; PLT, platelet count; PT, prothrombin time; PTT, activated partial thromboplastin time; PTX, paclitaxel; PTXNp, PTX nanoparticle; RBC, red blood cells; $T_{1/2}$, terminal half life; Vd, volume of distribution based on the terminal phase; WBC, white blood cells.

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