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ORIGINAL PAPER

# Biodegradable PEG-PCL Nanoparticles for Co-delivery of MUC1 Inhibitor and Doxorubicin for the Confinement of Triple-Negative Breast Cancer

Akanksha Behl[1] · Subhash Solanki[2] · Shravan K. Paswan[3] · Tirtha K. Datta[2] · Adesh K. Saini[4] · Reena V. Saini[4] · Virinder S. Parmar[5,6] · Vijay Kumar Thakur[7,8,9] · Shashwat Malhotra[10] · Anil K. Chhillar[1]

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## Abstract

Combating triple-negative breast cancer (TNBC) is still a problem, despite the development of numerous drug delivery approaches. Mucin1 (MUC1), a glycoprotein linked to chemo-resistance and progressive malignancy, is unregulated in TNBC. GO-201, a MUC1 peptide inhibitor that impairs MUC1 activity, promotes necrotic cell death by binding to the MUC1-C unit. The current study deals with the synthesis and development of a novel nano-formulation (DM-PEG-PCL NPs) comprising of polyethylene glycol-polycaprolactone (PEG-PCL) polymer loaded with MUC1 inhibitor and an effective anticancer drug, doxorubicin (DOX). The DOX and MUC1 loaded nanoparticles were fully characterized, and their different physicochemical properties, viz. size, shape, surface charge, entrapment efficiencies, release behavior, etc., were determined. With $IC_{50}$ values of 5.8 and 2.4 nm on breast cancer cell lines, accordingly, and a combination index (CI) of $< 1.0$, DM-PEG-PCL NPs displayed enhanced toxicity towards breast cancer cells (MCF-7 and MDA-MB-231) than DOX-PEG-PCL and MUC1i-PEG-PCL nanoparticles. Fluorescence microscopy analysis revealed DOX localization in the nucleus and MUC1 inhibitor in the mitochondria.

Further, DM-PEG-PCL NPs treated breast cancer cells showed increased mitochondrial damage with enhancement in caspase-3 expression and reduction in Bcl-2 expression.In vivo evaluation using Ehrlich Ascites Carcinoma bearing mice explicitly stated that DM-PEG-PCL NPs therapy minimized tumor growth relative to control treatment. Further, acute toxicity studies did not reveal any adverse effects on organs and their functions, as no mortalities were observed.

The current research reports for the first time the synergistic approach of combination entrapment of a clinical chemotherapeutic (DOX) and an anticancer peptide (MUC1 inhibitor) encased in a diblock PEG-PCL copolymer. Incorporating both DOX and MUC1 inhibitors in PEG-PCL NPs in the designed nanoformulation has provided chances and insights for treating triple-negative breast tumors. Our controlled delivery technology is biodegradable, non-toxic, and anti-multidrug-resistant. In addition, this tailored smart nanoformulation has been particularly effective in the therapy of triple-negative breast cancer.

**Keywords** PEG-PCL · Drug delivery system · Triple-negative breast cancer · Doxorubicin · MUC1 inhibitor · Bcl-xL

## Abbreviations

| | |
|---|---|
| P-GP | Poly-glycoproteins |
| DOX | Doxorubicin |
| IP | Intraperitoneal |
| PDI | Polydispersity index |
| EAT | Ehrlich ascites tumor |
| TEM | Transmission electron microscopy |
| TNBC | Triple-negative breast cancer |
| NP | Nanoparticle |

✉ Vijay Kumar Thakur
vijay.thakur@sruc.ac.uk

✉ Shashwat Malhotra
malhotra-shashwatmalhotra@gmail.com

✉ Anil K. Chhillar
anil.chhillar@gmail.com

Extended author information available on the last page of the article

## Introduction

TNBC differs from other types of invasive breast cancer in that it multiplies and transmits speedily. With a dismal prognosis, it has fewer therapy options. TNBC represents 15–25% of all breast cancer incidences, and it is associated

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