Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-022-01169-8

ORIGINAL ARTICLE

Development of doxorubicin hydrochloride–loaded whey protein nanoparticles and its surface modification with N-acetyl cysteine for triple-negative breast cancer

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Accepted: 18 April 2022

Abstract
Limited targeted therapies are available for triple-negative breast cancer (TNBC). Thus, the current research focused on developing a targeted protein nanoparticle for TNBC. First, the doxorubicin hydrochloride (Dox)–loaded genipin-crosslinked whey protein nanoparticles (WD) were prepared and optimised by the QbD method using BBD. The hydrodynamic diameter of WD was found to be 364.38 ± 49.23 nm, zeta potential −27.59 ± 1.038 mV, entrapment 63.03 ± 3.625% and Dox loading was found to be 1.419 ± 0.422%. The drug recovery after 18 months of storage was 69%. Then, it was incubated with NAC to obtain modified WD (CyWD). WD followed first-order release kinetics, whereas CyWD followed the Higuchi model. Hemagglutination and hemolysis were not found qualitatively in WD and CyWD. Upon injecting the nanoformulations to 4T1-induced mice, the highest efficacy was found to be in CyWD followed by WD and Dox injection. Upon histopathological observance, it was found that the CyWD group gave the most significant damage to the 4T1 tumour tissue. Thus, NAC-modified protein nanoparticles carrying chemotherapeutic agents can be an excellent targeted therapeutic system against TNBC.

Keywords Quality by Design · Box Behnken design · Genipin · Targeting · TNBC

Introduction

Triple-Negative Breast Cancer (TNBC) is one of the breast cancer types that lacks estrogen, progesterone and human epithelial growth factor 2 receptors. It holds a distinct molecular profile and also lacks targeted therapies [1].

Nanoparticles have gained much interest in several fields apart from therapeutics such as imaging, catalysis, electronics, energy harvesting, and mechanical industries [2]. Nanoparticulate drug delivery vehicles have overcome several issues related to conventional drug delivery systems, such as bioavailability, residence time and targeting issues [3]. Protein nanoparticles often hold the advantage of being biocompatible, biodegradable, easy to fabricate and have abundant natural resources as the starting material. Unlike nanoparticles from metallic or synthetic sources, the protein nanoparticles do not hold potential toxicity and are not rapidly cleared out [4].

Whey protein (WP) is a well-known protein obtained from a dairy source. It is a versatile nutritional source with excellent applications [5]. Besides this, its application in particulate forms has also been extensively studied, whether in its native or denatured form [6]. It is an antioxidant [7]. It can also be used as a pharmaceutical carrier [8]. Wei et al. formulated WP-zein nanoparticles by pH shifting method [9]. Giroux and Britten encapsulated hydrophobic aroma into

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Published online: 30 April 2022