UNIVERSITI TEKNOLOGI MARA (UiTM)

STUDY OF CELLULAR UPTAKE OF NOVEL DRUG FORMULATIONS FOR PACLITAXEL ON TRIPLE NEGATIVE BREAST CANCER CELLS (MDA-231)

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ABSTRACT

Paclitaxel is one of the most important drug of choice for cancer treatment. However, commercially available paclitaxel used in the current clinical setting is formulated in Cremophor EL, a solvent which has been reported to elicit a number of adverse side effects. Nanoparticle (NP) technology may provide a safer alternative for sustained chemotherapy. The aim of this work was to investigate the efficiency of cellular uptake of polymeric nanoparticles which were coated with poly methacrylic acid (PMAA), poly acrylic acid (PAA), and poly N-vinyl caprolactam (PNVCL) using an *in vitro* model (breast cancer triple negative MDA-231 cells). Coumarin-6 loaded polymeric nanoparticles were prepared by polymerization dispersion method. Coumarin-6 was used for the purpose of fluorescent labelling to assist in the detection of cellular uptake of nanoparticles by MDA-231 cells. In the present study, the use of fluorescence plate reader was utilized in quantifying the efficiency of cell uptake. Cellular uptake of coumarin-6 loaded nanoparticles by MDA-231 was highest (8.20%) in poly N-vinyl caprolactam (PNVCL), when compared to poly methacrylic acid (PMAA, 7.55%) or poly acrylic acid (PAA, 6.23%) nanoparticles. The PNVCL coated nanoparticles showed greater advantages *in vitro* compared to the other two formulations. Studies on PNVCL coated nanoparticles deserve further attention and more studies on its efficacy are important.

CHAPTER 1

INTRODUCTION

Cytotoxic drugs, used either as single agents or in combination therapies, have demonstrated anti-proliferative activity against metastatic breast cancer (Parkin, 2001). Unfortunately, their efficacy is often limited due to the administration of suboptimal dosages of these drugs in order to avoid chronic and acute toxicities. Intravenously administered therapeutic molecules also run the possibility of being removed from the circulation by a defence mechanism known as the reticulo endothelial system, which greatly reduces the circulation half-life of the drugs (Tanaka et al., 2009). Therefore, it would be ideal if the drugs can be developed as a targeted or localized drug delivery system in an effort to limit the occurrence of systemic toxicities associated with existing drug formulations (Trickler et al., 2009).

Paclitaxel, a compound extracted from the bark of *Taxus brevifolia*, is a particularly well known anticancer agent and has been clinically used in the treatment against a wide spectrum of cancers including ovarian, breast, and non-small-cell lung cancers, as well as AIDS-related Kaposi's sarcoma (Stevens et al., 2004). The compound binds to beta subunit of tubulin in microtubules causing polymerization of tubulin dimers and at the same time inhibiting depolymerization of the microtubules which subsequently leads to mitotic cell cycle arrest and cell death through apoptosis (Madaan et al., 2012). To date, there are only two commercially available paclitaxel formulations in the market: (1) Taxol®, paclitaxel dissolved in a mixture of Cremophor® EL and ethanol; and (2) Abraxane, injectable suspension of