PREPARATION AND CHARACTERIZATION OF QUERCETIN-LOADED FOLIC ACID TPGS MICELLES AGAINST MCF-7 BREAST CANCER CELL LINE

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ABSTRACT

Breast cancer is one of the common cancers in the world and possibility of this disease among women is higher. In recent years, variety of nanoparticles have been discovered and synthesized in such a way to increase the therapeutic efficiency of drugs through targeted area of tumor cells without causing any harm towards healthy tissues. Quercetin is a polyphenolic compound that exists in plants, fruits, and vegetables and has showed numerous promising health benefits. However, therapeutic applications of quercetin are limited due to its low water solubility and poor bioavailability. The main objectives of this study were to synthesize quercetin-loaded folic acid d-α-tocopheryl polyethylene glycol succinate (TPGS) polymeric micelles (QUE-FA-TPGS-PMs), to characterize the physicochemical properties of QUE-FA-TPGS-PMs and to analyze the *in vitro* cytotoxicity of QUE-FA-TPGS-PMs against MCF-7 breast cancer cells. The TPGS micelles containing quercetin were prepared by thin film hydration method and were characterized for their particle size, polydispersity (PDI), encapsulation efficiency (EE), drug loading (DL), critical micelle concentration (CMC), *in vitro* drug release, and *in vitro* cytotoxicity. Particle size and polydispersity were analyzed using a zetasizer while surface morphology was determined by transmission electron microscopy (TEM). The EE and DL were determined by ultraviolet-visible (UV-Vis) spectrophotometry while the *in vitro* drug release studies of micelles were carried out by dialysis bag diffusion method. The *in vitro* cytotoxicity was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay where the cell viability was measured after 24, 48 and 72 h of incubations. It was observed that the average size of both QUE-FA-TPGS-PMs were between 118.53 nm and 651.55 nm. This indicates that these PMs can escape reticuloendothelial system (RES) and have longer circulation in blood. The PDI values were recorded between 0.23 and 0.67 revealed that these PMs were stable. From the TEM results, it can be observed that the QUE-FA-TPGS-PMs were in a spherical shape. The QUE-FA-TPGS-10.0 displayed high EE of 99.80% with low CMC of 0.008%. The lower value of CMC indicates greater stability upon dilution. After 96 h, drug release from the QUE-FA-TPGS-10.0 reached 39.42% maximum cumulative percentage of quercetin release. This slower release of quercetin indicates the QUE-FA-TPGS-10.0 was able to be sustainably released. The QUE-FA-TPGS-10.0-PMs exhibited the lowest cell viability of 23.6% against MCF-7 cells after 72 h of incubation. From the findings, it can be concluded that quercetin was successfully loaded inside PMs. These QUE-FA-TPGS-PMs were able to specifically target MCF-7 cells, delivered quercetin inside MCF-7 cells and cause cytotoxicity, thus can supports their role as a new targeted drug delivery system against MCF-7 breast cancer cells.

ABSTRAK

Kanser payudara adalah salah satu kanser biasa di dunia dan kebarangkalian penyakit ini di kalangan wanita adalah lebih tinggi. Dalam beberapa tahun kebelakangan ini, pelbagai partikel nano telah ditemui dan disintesis untuk meningkatkan kecekapan teraputik ubat-ubatan pada kawasan sasaran sel-sel tumor tanpa menyebabkan sebarang kemudaratan terhadap tisu yang sihat. *Quercetin* adalah sebatian polifenolik yang wujud dalam tumbuhan, buah-buahan, dan sayur-sayuran dan telah menunjukkan banyak manfaat kesihatan. Walau bagaimanapun, aplikasi teraputik *quercetin* adalah terhad kerana kelarutan air yang rendah dan ketersediaan bio yang lemah. Objektif utama kajian ini adalah untuk mensintesis misel polimer asid folik d-α-tocopheryl polietilena glikol suksinat (TPGS) yang dimuatkan dengan *quercetin* (QUE-FA-TPG-PMS), untuk mencirikan sifat fizikokimia QUE-FA-TPGS-PMs dan untuk menganalisis sitotoksin *in vitro* QUE-FA-TPGS-PM terhadap sel-sel kanser payudara MCF-7. Misel TPGS yang mengandungi *quercetin* telah disediakan oleh kaedah penghidratan filem nipis dan saiz zarah, serakan poli (PDI), kecekapan pengkapsulan (EE), pemuatan dadah (DL), kepekatan misel kritikal (CMC) pelepasan dadah *in vitro*, dan sitotoksin *in vitro* telah dicirikan. Saiz zarah dan serakan poli dianalisis menggunakan zetasizer manakala morfologi permukaan ditentukan oleh analisis mikroskopi elektron penghantaran (TEM). EE dan DL ditentukan oleh spektrofotometri keterlihatan violet ultra (UV-Vis) manakala pelepasan dadah *in vitro* dijalankan oleh kaedah penyebaran beg dialisis. Sitotoksin *in vitro*, dinilai menggunakan3-(4,5- dimetilthiazol-2-yl)-2,5-difeniltetrazolium bromida (MTT) cerakin di mana daya maju sel diukur selepas 24, 48 dan 72 jam inkubasi. Diperhatikan bahawa saiz purata kedua-dua QUE-FA-TPGS-PMs adalah antara 118.53 nm dan 651.55 nm. Ini menunjukkan bahawa PMs ini dapat menghindari sistem retikuloendotelium (RES) dan mempunyai peredaran yang lebih lama dalam darah. Nilai serakan poli direkodkan diantara 0.23 dan 0.67 mendedahkan bahawa PMs ini stabil. Daripada keputusan TEM, dapat dilihat bahawa QUE-FA-TPGS-PMs berada dalam bentuk sfera. QUE-FA-TPGS-10.0 menunjukkan EE yang tinggi iaitu 99.80% dengan CMC yang rendah sebanyak 0.008%. Nilai CMC yang lebih rendah menunjukkan kestabilan yang lebih besar setelah dicairkan. Selepas 96 jam, pelepasan dadah dari QUE-FA-TPGS-10.0 mencapai 39.42% peratusan kumulatif maksimum pelepasan *quercetin*. Pelepasan *quercetin* yang lebih perlahan ini menunjukkan QUE-FA-TPGS-10.0 dapat dikeluarkan secara mampan. QUE-FA-TPGS-10.0 mempamerkan daya maju sel yang paling rendah 23.6% terhadap sel MCF-7 selepas 72 jam inkubasi. Dari penemuan, ini dapat disimpulkan bahawa *quercetin* berjaya dimuatkan di dalam PMs. QUE-FA-TPGS-PMs dapat mensasarkan sel-sel MCF-7 secara khusus, menyampaikan *quercetin* ke dalam sel MCF-7 dan menyebabkan sitotoksik, dengan itu dapat menyokong peranan mereka sebagai sistem baru penyampaian dadah yang disasarkan terhadap sel-sel kanser payudara MCF-7.

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LIST OF ABBREVIATIONS

BC	-	Breast cancer
Bcl-2	-	B-cell lymphoma 2
CMC	-	Critical micelle concentration
CNS	-	Central nervous system
CO2	-	Carbon dioxide
CT	-	Chemotherapy
CUR-PM	-	Curcumin-loaded polymeric micelles
DDs	-	Drug delivery system
DES	-	Deep eutectic solvents
DL	-	Drug loading
DMEM	-	Dulbecco's Modified Eagle's Medium
DMSO	-	Dimethyl sulfoxide
DNA	-	Deoxyribonucleic acid
DOX	-	Doxorubicin
DTX	-	Docetaxel
DTX-TPGS-Tf1	-	DTX-loaded transferrin-targeted micelles
EE	-	Encapsulation efficiency
EDC	-	Dimethlyaminopropyl carbodiimide
EMA	-	European Medicines Agency
EPR	-	Enhanced permeability and retention
ER	-	Estrogen receptor
ERBB2+	-	Epidermal growth factor receptor 2-positive
ET	-	Endocrine therapy

FA	-	Folic acid
FBP	-	Folate binding protein
FBS	-	Fetal bovine serum
FDA	-	Food and Drug Administration
FRs	-	Folate receptors
FTIR	-	Fourier transform infrared spectroscopy
h	-	Hour
HER2	-	Human epidermal growth factor receptor 2
HPEE-PTX	-	Hyperbranched poly(ether-ester) paclitaxel
HR+/ERBB2-	-	Hormone receptor-positive and HER2-negative
HA	-	Hyaluronic acid
IARC	-	International Agency for Research on Cancer
IC	-	Inhibitory concentration
IHC	-	Immunohistochemistry
IR	-	Infrared radiation
LDH	-	Lactate dehydrogenase
LMPM	-	Lecithin-based mixed polymeric micelle
MCF-7	-	Human breast cancer cell line
MDR	-	Multidrug resistance
mPEG-PDLLA-Phe(Fmoc))	-	monomethoxy poly(ethylene glycol)-block-poly(D,Llactide)-phenylalaninefluorenylmethoxy carbonyl
mPEG-PCL-PDMA	-	methyl (polyethylene glycol)-block-polycaprolactone poly(dopamine methacrylamide)
mPEG-PCL-PVBA	-	methyl (polyethylene glycol)-block-polycaprolactone poly(vinylphenylboronic acid
MPS	-	Mononuclear phagocyte system
mRNA	-	Messenger ribonucleic acid

MTT	-	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADH	-	Nicotinamide adenine dinucleotide
NHS	-	N-hydroxysuccinimide
NTP	-	National Toxicology Program
NPs	-	Nanoparticles
OD	-	Optical density
PBS	-	Phosphate buffer saline
PCL	-	Polycaprolactone
PCL NPs	-	Polycaprolactone nanoparticles
PCS	-	Photon Correlation Spectroscopy
PDI	-	Polydispersity index
PGA	-	Polyglutamic acid
P-gp	-	P-glycoprotein
PMs	-	Polymeric micelles
PEG	-	Polyethylene glycol
PLA	-	Poly (lactic acid)
PLA-PEG	-	Poly(lactic acid)−poly(ethylene glycol)
PLB	-	Plumbagin
PLGA	-	Poly (lactic-co-glycolide)
PR	-	Progesterone receptor
PT	-	Pteridine
PTX	-	Paclitaxel (PTX)
P4	-	Passage 4
P5	-	Passage 5
P7	-	Passage 7
QUE	-	Quercetin
QUE-FA-TPGS-PM	-	Quercetin-loaded folic acid-TPGS polymeric micelles
QUE-CS-DOX	-	Quercetin-chitosan conjugated doxorubicin

RES	-	Reticuloendothelial system
ROS	-	Reactive oxygen species
RT	-	Radiotherapy
SEM	-	Scanning Electron Microscopy
TEA	-	Triethylamine
TEM	-	Transmission electron microscopy
TOS	-	Tocopheryl succinate
TPGS	-	D-a-tocopheryl polyethylene glycol succinate (TPGS)
TK	-	Tyrosine kinase
5-FU	-	5-fluorouracil

LIST OF SYMBOLS

bw	-	body weight
cm^{-1}	-	centimeter
d	-	day
°C	-	degree celsius
g	-	gram
kg	-	kilogram
<	-	less than
mg	-	milligram
mL	-	millimeter
nm	-	nanometer
%	-	percentage
±	-	plus or minus
w/v	-	weight per volume

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CHAPTER 1

INTRODUCTION

1.1 Background of The Study

Cancer is one of the common diseases in the world after cardiovascular diseases and the probability of one getting cancer has been increasing day by day (Allahverdiyev *et al.,* 2018). Breast cancer (BC) is one of the leading cancers in the world and women showed the highest mortality rate (Nounou *et al.,* 2015). Literally, 40 000 women are losing their lives due to this BC problem and most of them are diagnosed with metastatic cancer. Due to that, BC has been ranked as a disease with a higher death rate (Ferlay *et al.,* 2018; Lovitt *et al.,* 2018; Vera-Ramirez *et al.,* 2018; Guo *et al.,* 2019). The common BC treatments include surgery, chemotherapy (CT), and radiotherapy (RT). However, the effects of these procedures may affect healthy cells too (Akbarian *et al.,* 2020). Anticancer drugs such as doxorubicin (DOX) and docetaxel (DTX) have been used in CT and these drugs exhibited cytotoxic effects on both healthy and cancer cells (Alibolandi *et al.,* 2016; Fraczkowska *et al.,* 2018).

Targeted drug delivery system (DDS) has been introduced for cancer treatment (Thu *et al.,* 2015). A targeted DDS is a system that releases drugs at target cells in a controlled manner. This method has been exploited to increase therapeutic concentration towards selected target site and control the movement of drug to normal cells, thus reduces undesirable effects (Jain *et al.,* 2014; Khattabi *et al.,* 2017). Besides, DDS are established to enhance the level of solubility and bioavailability of hydrophobic drug molecules (Patra *et al.,* 2018b). Nanoparticles (NPs) such as polymeric micelles (PMs), liposomes, nanospheres, dendrimers, polymer-drug conjugate, and solid lipid nanoparticles act as a promising drug delivery platform for cancer treatment (Tran *et al.,* 2017; Allahverdiyev *et al.,* 2018; Barani *et al.,* 2021; Sezgin-Bayindir *et al.,* 2021).

Polymeric micelles (PMs) are nanosized colloidals composed of amphiphilic block copolymers of hydrophilic shell and hydrophobic core (Kapse *et al.,* 2020). For instance, DOX has been loaded in bicomponent micelles of methyl (polyethylene glycol)-block-polycaprolactone poly(dopamine methacrylamide), poly(vinylphenylboronic acid) (mPEG-PCL-PDMA/mPEG-PCL-PVBA) to form PMs with the size ranging from 47.61 nm to 65.99 nm (Wang *et al.,* 2020a). Similarly, paclitaxel (PTX) has been loaded in monomethoxy poly(ethylene glycol)-block-poly(D,Llactide)-phenylalaninefluorenylmethoxy carbonyl (mPEG-PDLLA-Phe(Fmoc)) PMs and has been shown to have antitumor efficacy against nude mice bearing Bel-7402 tumor (Deng *et al.,* 2018). These PMs were reported to have controlled drug release, prolonged systemic circulation and high stability in bloodstream (Deng *et al.,* 2018; Wang *et al.,* 2020a).

Flavonoids are present in the nature form of benzo-γ-pyrone derivatives. The major sources of these compounds are plants, vegetables, and flowers (Rauf *et al.,* 2018; Ward *et al.,* 2018). They exhibit beneficial therapeutic properties and can provide protection to the human body from harmful infection and cancer (Panche *et al.,* 2016). Quercetin (QUE) is one of the flavonoids chemically identified as 3,3′,4′,5,7- pentahydroxyflavone ($C_{15}H_{10}O_7$). QUE has antioxidant activity, thus it is useful for the treatment of several diseases and for cancer prevention (Iacopetta *et al.,* 2017). Earlier study observed that QUE treatment given to the A549 human lung cancer and MDA-MB-468 breast cancer cell lines has resulted in reduced availability of these cells than when treated with free QUE (Baksi *et al.,* 2018). QUE has also been loaded in the form of PMs using hyaluronic acid (HA) and DTX against hepatocellular carcinoma cell line (HepG2) cells. It was reported that these DTX/HA-QUE PMs have resulted in cancer cell apoptosis and could downregulate the P-glycoprotein (P-gp) expression in tumor cells (Xu *et al.,* 2016).

Folic acid (FA), also known as vitamin B1 complex, is an oxidized form of folate. It is a natural ligand of folate receptor, nontoxic, highly biocompatible and stable under long term storage or in blood circulation (Alibolandi *et al.,* 2016; Xiong

et al., 2019). It has many biological functions including assisting intestinal absorption and metabolism in the liver (Steluti *et al.,* 2019). Folic acid is an important vitamin for the biosynthesis of nucleotide bases and is required within the cell to carry out one carbon methylation reaction (Hou *et al.,* 2020). Besides, folate receptors (FRs) have been overexpressed in several human cancer cells such as breast, ovarian, brain, kidney, and lung (Hao *et al.,* 2017).

It was stated that the expression level of FRs was higher in tumors than in normal tissue (Luong *et al.,* 2017). Due to this, FA has been employed as a targeting moiety for targeted DDS of several anticancer agents with the aim to prevent any nonspecific attack on normal tissues (Hao *et al.,* 2017). For instance, DOX has been carried in the poly(lactic acid)−poly(ethylene glycol)-folate polymeric micelle and was shown to have higher cytotoxicity against SKOV3 human ovarian cancer cells than the DOX-loaded PM without folate as the targeting ligand (Hami *et al.,* 2014).

D-a-tocopheryl polyethylene glycol succinate (TPGS) or so-called vitamin E TPGS is a derivative of natural vitamin E (alpha tocopherol) which is conjugated to polyethylene glycol (PEG) 1000 (Luiz *et al.,* 2021; Li *et al.,* 2019). It has an amphiphilic nature due to the presence of a hydrophilic polar head and a lipophilic alkyl tail, similar to a conventional surfactant (Lu *et al.,* 2019; Kujar *et al.,* 2020). TPGS is nonionic and highly hydrophilic. Its bulky structure and large surface area give out tremendous effects on the level of solubilizer and it can act as a bioavailability enhancer of hydrophobic drugs (Pawar *et al.,* 2016; Yang *et al.,* 2018). The lipophilic portion of TPGS allows poorly soluble drug solubilized in the PMs (Chen *et al.,* 2020a; Wang *et al.,* 2020b). TPGS can also enhance cellular uptake of nanoparticle formulation and prolong blood circulation time of the drug-loaded micelles in animal models (Hao *et al.,* 2017).

1.2 Problem Statement

Chemotherapy (CT) is a common treatment that has been used for treating cancer cells. Anticancer drugs such as DOX and 5-fluorouracil (5-FU) are delivered to patients to kill the uncontrolled proliferation of tumor cells (Deveci *et al.,* 2017; Tan and Norhaizan, 2019; Zong *et al.,* 2019). Due to nonspecific targeting by the anticancer agents, the poor drug delivery resulted in adverse side effects towards normal cells such as elevated toxicity in normal cells and an increased incidence of multiple drug resistance (Tran *et al.,* 2017; Senapati et *al.,* 2018). The side effects of CT may come from the drug itself or its dosage level because of the adjuvant toxicity and restricted pharmacokinetics (Zhao *et al.,* 2018).

QUE showed numerous promising health benefits such as anticancer, anti-inflammatory, antioxidant, anti-proliferative, antimicrobial, and antidiabetic (Baksi *et al.,* 2018; Ismail *et al.,* 2018; Ghayour *et al.,* 2018; Salehi *et al.,* 2020). Its anticancer activities were shown related to prevention of tumorigenesis and induction of p53 phosphorylation (Elsayed *et al.,* 2021). However, it is hydrophobic, and its therapeutic applications are limited due to its low water solubility and poor bioavailability (Zhang *et al.*, 2016). Therefore, QUE requires a suitable carrier to increase its water solubility and bioavailability in the bloodstream. QUE showed advantages over other drugs such as docetaxel (DTX) and doxorubicin (DOX) as QUE could reverse DTX resistance in prostate cancer cells while DOX usage is limited due to the risk of severe cardiotoxicity (Chang *et al.,* 2018; Lu *et al.,* 2020). PMs have been shown as promising drug carriers and they are commonly synthesized using block copolymers using hydrophilic polymer such as PEG, and hydrophobic polymer such as polycaprolactone (PCL) (Park *et al.,* 2021; Xia *et al.,* 2021; Yang *et al.,* 2021). Thus, the use of a single amphiphilic polymer such as TPGS to form PM needs to be further explored.

DDS without targeting ligand showed several drawbacks such as dose-limiting side effects, poor bioavailability and solubility, non-specific interactions, off-site toxicity, and damages to healthy cells (Liyanage *et al.,* 2019; Arslan *et al.,*

2021). The concentration and efficacy of delivered NP anticancer drug without ligand at cancer cell was reduced due to delivery of drug to normal cells (Hafeez *et al.,* 2021). Generally, NPs sizes of 10 to 100 nm are suitable for cancer therapy and could effectively deliver drugs and attain enhanced permeability and retention (EPR) effect (Senapati *et al.,* 2018; Yao *et al.,* 2020). Size larger than 100 nm is likely to be cleared from circulation by the reticuloendothelial system (RES) (Yao *et al.,* 2020).

High doses of QUE (50 mg kg^{-1} body weight (bw) per day for 14 days) has shown adverse effects on thyroid function in rats (Andres *et al.,* 2018). This study showed a decrease in radioiodine uptake by the thyroid after intraperitoneal quercetin application. However, the adverse effects on thyroid hormone were not observed in animal models for obesity and hypothyroidism studies involving oral application of QUE at doses between 10 and 25 mg kg^{-1} bw per day for 2–6 months (Baldissarelli *et al.,* 2016; Cheserek *et al.,* 2016). In other study, QUE were applied orally on a DOX-induced rat model for nephrotoxicity (Heeba and Mahmoud, 2016). QUE doses of 10, 50 and 100 mg kg^{-1} bw per day were applied for 14 days and intraperitoneal injection of DOX of 15 mg kg^{-1} bw were applied on day 7. Low dose of 10 mg kg^{-1} bw QUE was found preserving renal function while highest QUE dose of 100 mg kg^{-1} bw showed pro-oxidative and pro-inflammatory effects resulting in renal dysfunction (Heeba and Mahmoud, 2016). However, QUE did not show toxicity in some other studies (Sadhukhan *et al.,* 2019). In this study, the targeted DDS will not enhance toxicity of QUE as the amount delivered is very little. Also, the PMs are composed of TPGS which helps in amplify the anticancer effects of quercetin and FA as targeting ligand helps in bringing these PMs to tumor sites via active targeting.

However, surface modification on NPs that are coated with hydrophilic materials such as PEG lessens the opsonization and affects their bioavailability and half-life (Yao *et al.,* 2020). Thus, this could avoid clearance by the immune system. Increase in drug concentration does not impact NP as large sizes are capable of retention in tumor tissue than those with smaller sizes (Yu *et al.,* 2020). Furthermore, sustained release of a drug is important to prolong the therapeutic effect over an

extended period at targeted area (Sharma *et al.,* 2019). Moreover, it was reported that increase in drug concentration and exposure time, resulted in larger micelles size, and increase the cytotoxicity against Caco-2 cell line of colon carcinoma (Mu *et al.,* 2019).

1.3 Objectives of Study

The objectives of this study were:

i. To synthesize quercetin-loaded folic acid-TPGS polymeric micelles (QUE-FA-TPGS-PMs) at different quercetin concentrations.
ii. To characterize the physicochemical properties of quercetin-loaded folic acid-TPGS polymeric micelles (QUE-FA-TPGS-PMs).
iii. To analyze the in vitro cytotoxicity of quercetin-loaded folic acid-TPGS polymeric micelles (QUE-FA-TPGS-PMs) against MCF-7 breast cancer cells.

1.4 Scope of Study

The PMs were synthesized by first conjugating folic acid (FA) to the TPGS polymer. Three samples of QUE-loaded folic acid-TPGS polymeric micelles (QUE-FA-TPGS PMs) were prepared by thin film hydration method in different concentrations. These QUE-FA-TPGS PMs were further characterized using a zeta sizer, transmission electron microscope (TEM), Fourier transform infrared spectroscopy (FTIR), and UV-vis spectrophotometry to determine their particle size, polydispersity index (PDI), structural composition, critical micelle concentration (CMC), encapsulation efficiency (EE), drug loading (DL) content and *in vitro* drug release. These QUE-FA-TPGS PMs were then tested for their *in vitro* cytotoxicity using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay against MCF-7 breast cancer cells for 24, 48 and 72 h.

1.5 Significance of Study

In this study, a targeted DDS was successfully developed by loading QUE in the TPGS single polymer to form PM. The synthesized QUE-TPGS-PMs conjugated with FA resulted in cytotoxicity of MCF-7 breast cancer cells. This indicates that the hydrophilic PEG of TPGS and folic acid as the ligand are able to deliver QUE, which is hydrophobic, towards the targeted cancer cells. This study revealed that QUE-FA-TPGS-PMs can deliver QUE in a sustained manner. The results revealed that low QUE concentrations displayed smaller micelles which can prevent RES clearance. The presence of TPGS in this PM structure will increase anticancer effects of QUE and increase circulation time in bloodstream while FA helps in carrying these PMs to tumor sites via active targeting. Therefore, this study suggested that QUE-FA-TPGS PMs can be considered as a potential targeted DDS for breast cancer treatment as shown against MCF-7 breast cancer cells to reduce the side effects of chemotherapy drugs.

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