RESEARCH PAPER

Investigation of the In Vitro Release Dynamics of Doxorubicin and Paclitaxel Loaded Polymeric and Lipid Nanocarriers for Breast Cancer Therapy

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Abstract
Doxorubicin (DOX) and paclitaxel (PTX) are still two of the most clinically relevant cytotoxic drugs for the treatment of breast cancer, but both drugs have therapeutic indices limited by low aqueous solubility, non-specific biodistribution, and dose limiting toxicity like hypersensitivity reactions and cardiotoxicity. Nanocarrier-based drug delivery systems, especially polymeric nanoparticles and lipid-based nanocarriers have been widely explored to overcome these limitations in order to achieve controlled and sustained drug release, to improve the solubilisation of these drugs, and to favour their uptake into the tumour tissue through EPR. In the present work, the in vitro release profiles of polymeric (PLGA) and lipid-based (liposomal and solid lipid) nanocontainers loaded with DOX and PTX for breast cancer therapy have been reviewed and compared with each other. The profiles obtained by the dialysis membrane method under simulated physiological conditions (phosphate-buffered saline, pH 7.4 and 37 ± 0.5 °C) were analysed and fitted with zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models to explore the mechanism and the rate of drug release. Lipid-based nanocarriers showed more sustained release with a smaller initial burst release, which could be explained by the partitioning-controlled diffusion of the drug across the lipid bilayer or the matrix, while polymeric nanocarriers had a higher release rate in the initial phase, followed by a sustained release due to matrix erosion and diffusion. The release exponents (n) from Korsmeyer-Peppas model showed a predominantly Fickian diffusion controlled mechanism and both drug-carrier combinations best fitted Higuchi model. The results confirm the need for the optimization of the release profile of the drugs released from these nanocarriers, which can be achieved through proper formulation, and provide further rationale for using nanocarriers for the delivery of DOX and PTX in breast cancer patients in order to achieve the best therapeutic effect with the minimum systemic toxicity.

Keywords - Doxorubicin, paclitaxel, nanocarriers, PLGA nanoparticles, liposomes, drug release kinetics, Korsmeyer-Peppas model, breast cancer therapy

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1. Introduction

Breast cancer remains the most common cancer in women and a major cause of cancer death in women in the world. Systemic chemotherapy is an essential treatment in the neoadjuvant, adjuvant, and metastatic treatment of breast cancer and is the most effective treatment for breast cancer; anthracyclines and taxanes are most commonly used in the majority of standard care treatments. While these, doxorubicin (DOX) and paclitaxel (PTX), are two of the most widely used cytotoxic drugs, they both have broad-spectrum antitumour activity and well-defined mechanisms of action. Both agents have been shown to be clinically effective, but they each have important drawbacks which limit their therapeutic index.

The main limitation of doxorubicin is dose-dependent, cumulative cardiotoxicity, and therefore the maximum cumulative dose of the drug that can be given to a patient is limited. The taxanes are extremely poorly soluble in water and a derivative of paclitaxel, called paclitaxel albumin, has been formulated with Cremophor EL, a solubilising agent that has been associated with severe hypersensitivity reactions and peripheral neuropathy. Furthermore the both drugs are non-selective in tissue distribution and healthy rapidly dividing tissues are exposed to cytotoxic doses leading to off-target toxicities like myelosuppression, gastrointestinal toxicity and alopecia.

To overcome these limitations, drug delivery with nanotechnology has come to the fore as a rational approach. Nanoscale carriers can be used to modify the pharmacokinetic behaviour, increase the solubility, shield the drug from early degradation, and take advantage of the enhanced permeability and retention (EPR) effect that is typical of solid tumour vasculature, to achieve passive tumour targeting that encapsulates DOX and PTX. In this regard, two main types of nanocarriers have been the most prevalent ones

reported in the literature, such as polymeric nanoparticles, which are usually made of biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) or lipid-based nanocarriers such as liposomes or solid lipid nanoparticles (SLNs). Both platforms have already been clinically translated, with the examples of liposomal doxorubicin (Doxil® / Caelyx®) and albumin-bound paclitaxel (Abraxane®) for publications related to their release behaviour.

The in vitro drug release profile is a critical parameter for any nanocarrier system, as it can offer a valuable insight into the in vivo release behaviour, help to optimise the formulation, and can be used as a quality control parameter during pharmaceutical development. If the release is by diffusion, erosion, swelling or a combination of these mechanisms, the understanding of the mechanism will enable the rational design of the carriers with desired release kinetics that correspond to the desired therapeutic windows.

This paper studies and compares the in vitro drug release of DOX- and PTX-loaded polymeric and lipid nanocarriers developed for breast cancer therapy. The specific aims of this work are: (i) summarising the pharmacological rationale for nanocarrier-mediated delivery of DOX and PTX; (ii) describing representative formulation and in vitro release methodologies used for both polymeric and lipid-based nanocarriers; (iii) presenting and comparing simulated/representative cumulative release profiles for both drugs across the two carrier platforms; and (iv) applying established mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) to elucidate the underlying release mechanisms from which a framework for future formulation design of breast cancer-directed nanomedicines can be developed.

2. Doxorubicin and Paclitaxel: Pharmacological Profile as Anticancer Agents

2.1 Doxorubicin

Doxorubicin hydrochloride is an anthracycline antibiotic that was originally extracted from Streptomyces peucetius var. caesius, and is one of the most effective broad-spectrum antineoplastic agents used in clinical practice. It has several complementary mechanisms of action which contribute to its cytotoxicity in tumour cells, but which are also the main mechanisms responsible for the dose-limiting cardiotoxicity in cardiac myocytes: intercalation of its planar anthraquinone ring between pairs of DNA bases, which distorts the DNA helix and blocks both DNA replication and transcription; inhibition of topoisomerase II, an enzyme involved in untangling the supercoil structure of DNA during its replication; generation of the reactive oxygen species (ROS) by redox cycling of the quinone moiety.

Doxorubicin itself is water-soluble (as the hydrochloride salt), but occurs with a short plasma half life and a large volume of distribution, causing quick non-specific tissue distribution. DOX containing regimens (AC, FAC) are commonly used in breast cancer both in the adjuvant and metastatic setting and especially in triple negative and HER2 positive breast cancer. However, cumulative cardiotoxicity (usually in the form of dilated cardiomyopathy and congestive heart failure) limits lifetime dosing (usually around 450-550 mg/m² cumulative dose) and interventions that spare the heart whilst maintaining tumour exposure are therefore of great clinical interest. This constraint directly led to the development of liposomal formulation of DOX which modify the biodistribution of the drug and substantially decrease the cardiotoxic exposure while keeping, and sometimes even enhancing, antitumour activity.

2.2 Paclitaxel

Paclitaxel is a diterpenoid taxane isolated from the bark of the Pacific yew (Taxus brevifolia) whose mode of action is different from that of doxorubicin. Paclitaxel does not directly interact with the DNA molecule, but it binds to the β-subunit of tubulin in assembled microtubules and prevents the normal depolymerisation of the microtubules. This instability of the mitotic spindle causes cells to become arrested in G2/M of the cell cycle and ultimately leads to cell death by apoptosis. Rapidly dividing cancer cells are especially sensitive to the processes of mitotic spindle dynamics, making paclitaxel a potent antiproliferative agent with activity against a wide variety of solid cancers such as breast, ovarian and non-small-cell lung cancers.

The major formulation problem with paclitaxel is its extreme aqueous insolubility (around 0.3 μg/mL), which in the past, had to be overcome by solubilisation in a 1:1 solution of the Cremophor EL and dehydrated ethanol (the traditional Taxol® formulation). Cremophor EL has been known to cause acute hypersensitivity reactions, requiring premedication with corticosteroids and antihistamines, and has been reported to affect the pharmacokinetics of co-administered paclitaxel by the micelle entrapment of paclitaxel in plasma. The disadvantages led to the development of Cremophor-free delivery systems, such as nanoparticle albumin-bound paclitaxel (nab-paclitaxel, Abraxane®), and a multitude of experimental polymeric and lipid-based nanoparticulate carriers that are currently being investigated in academia and in clinical or translational research.

3. Nanocarrier-Based Drug Delivery Systems

3.1 Polymeric Nanocarriers

Polymeric nanoparticles are polymeric and of submicroscopic particles sizes from 10 to 1000 nm, which are also biodegradable and biocompatible. Poly(lactic-co-glycolic acid) (PLGA) is the most widely investigated polymer for anticancer drug delivery due to its FDA approval, tunable degradation rate (by changing the lactide/ glycolide ratio and molecular weight) and hydrolytic degradation into the nontoxic lactic acid and glycolic acid monomers that enter normal metabolic pathways. The other polymers used are polycaprolactone (PCL), chitosan, poly(alkyl cyanoacrylate) and PLGA-PEG copolymers which give a 'stealth' character that decreases the opsonisation and systemic circulation time.

Typical methods for preparation of polymeric nanoparticles include nanoprecipitation, single emulsion/solvent evaporation, and salting-out methods. The drug release from these systems is controlled by the diffusion of the drug from the polymer matrix, polymer swelling, and bulk or surface erosion of the polymer as it breaks down due to hydrolytic degradation, which usually results in the characteristic biphasic drug release: a burst release related to the release of surface-associated or loosely entrapped drug, and a sustained release related to the diffusion of the drug through the polymer matrix and bulk or surface erosion of the polymer as it breaks down during hydrolysis.

3.2 Lipid-Based Nanocarriers

There are three types of lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Vesicular system: liposomes: composition is composed of one or more phospholipid bilayers enclosing an aqueous core and can encapsulate hydrophilic drugs (in the aqueous core, e.g., DOX·HCl) and lipophilic drugs (within the phospholipid bilayers, e.g., PTX). The modification of the surface with polyethylene glycol (PEGylation) yields long-circulating 'stealth' liposomes, such as the clinically approved pegylated liposomal doxorubicin (Doxil®/Caelyx®) which significantly changes the biodistribution of DOX, and greatly decreases cardiotoxicity compared to free drug.

Solid lipid nanoparticles (SLN) are particles consisting of a solid lipid core (glyceryl monostearate, stearic acid, compritol) surrounded by surfactants in an aqueous dispersion, and have the benefits of being physically stable, easy to prepare on a large scale and not containing organic solvents in some preparation methods. A second generation of these, called nanostructured lipid carriers, contain a mixture of solid and liquid lipids, which form an imperfect crystal matrix by which a higher amount of the drug could be loaded and its expulsion during storage reduced. The release from lipid-based carriers is mostly controlled by the partitioning of the drug between the lipid and the release medium, lipid matrix or bilayer diffusion and, for SLNs, by the crystallinity of the lipids, generally giving a slower and more extended release curve than similar polymeric based systems, especially for lipophilic drugs like paclitaxel.

3.3 Rationale for Nanocarrier-Mediated Delivery of DOX and PTX in Breast Cancer

Hydrophilic and lipophilic nanocarriers are rationalized in the delivery of DOX and PTX in the treatment of breast cancer for a number of reasons. First, the apparent aqueous solubility of poorly soluble PTX is enhanced with the aid of nanoencapsulation, without the need of toxic solubilising vehicles like Cremophor EL. Second, both carriers can be used to passively accumulate in the tumour by the EPR effect: The poorly formed vascular structures and impaired lymphatic drainage of solid breast tumours allow nanoparticles in the size range of 20-200 nm to extravasate into the tumour, and to stay there. Third, the controlled release of the nanocarrier matrix and sustained release of the cytotoxic drug in the tumour for extended periods of time means that peak plasma levels of the drug linked to acute toxicities (such as cardiotoxicity and hypersensitivity) will be lower, leading to a potential improvement in the therapeutic index. Last but not least, both platforms can be surface functionalised with targeting ligands (folate, transferrin, trastuzumab and other antibodies targeting HER2, or hyaluronic acid for targeting CD44), which can be added to the passive EPR-mediated accumulation, especially of interest for aggressive subtypes like triple-negative and HER2-positive breast cancer.

4. Materials and Methods

4.1 Materials

The model anti-cancer drugs were doxorubicin hydrochloride and paclitaxel (analytical/pharmaceutical grade). Representative polymeric carriers used were poly(lactic-co-glycolic acid) (PLGA, 50:50, MW ~ 40-75 kDa) with polyvinyl alcohol (PVA) as stabiliser, and representative lipid carriers consisted of soy phosphatidylcholine and cholesterol (liposomes) or glyceryl monostearate, lecithin and poloxamer 188 (solid lipid nanoparticles). All phosphate-buffered saline (PBS, pH 7.4), dialysis membrane (MWCO 12-14 kDa), and organic solvents (dichloromethane, acetone and ethanol) were used as purchased.

4.2 Preparation of Nanocarriers

The PTX was loaded in polymeric nanoparticles using the single emulsion (oil-in-water) solvent evaporation method, while the more hydrophilic DOX·HCl was loaded in the double emulsion (water-in-oil-in-water) solvent evaporation method. In brief, the drug and

polymer were dissolved/dispersed in an organic solvent (dichloromethane or acetone), and emulsified into an aqueous PVA solution using high-speed homogenisation or probe sonication. This organic solvent was then evaporated under stirring and the nanoparticles were recovered by ultracentrifugation, washed and lyophilised.

A thin-film hydration method was used to prepare liposomal formulations, by dissolving phospholipid and cholesterol in chloroform-methanol and drying them under reduced pressure to form a thin lipid film that was then hydrated with an aqueous buffer containing the drug and subjected to sonication or membrane extrusion to form unilamellar vesicles of the desired size. Solid lipid nanoparticles were formed by hot high-pressure homogenisation (HPH) or emulsification-solvent evaporation (EE) method, where the drug was dissolved in the molten form of the selected lipid and dispersed in a hot aqueous surfactant solution, and then the mixture was cooled to facilitate the crystallisation of the lipid and the formation of SLNs.

4.3 Physicochemical Characterization

Mean particle size and polydispersity index (PDI) were determined by dynamic light scattering (DLS); zeta potential by laser Doppler electrophoresis; morphology by transmission or scanning electron microscopy (TEM/SEM); entrapment efficiency (EE%) was determined by measuring the amount of free (unentrapped) drug after separation using ultracentrifugation or dialysis, which was subsequently quantified spectrophotometrically or by HPLC and calculated as: EE% = [(Total drug - Free drug) / Total drug] × 100.

4.4 In Vitro Drug Release Study

An in vitro release study was performed in the dialysis membrane (bag) method in sink condition. A specific amount of the nanoparticle solution (with a fixed amount of DOX or PTX) was inserted in a pre-soaked dialysis membrane (MWCO 12-14 kDa) and sealed. The dialysis bag was suspended in phosphate buffered saline (pH 7.4, with 0.1-0.5% Tween 80 used for PTX formulations to ensure that the drug was in sink condition) and shaken on a magnetic stir plate or orbital shaker at 37 ± 0.5 °C at 50-100 rpm to simulate physiological conditions. Aliquots of the release medium were removed at certain time periods (0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h) and immediately replaced with an equal volume of freshly-prepared medium, which was brought to the same temperature, to maintain sink conditions. The drug amount in the withdrawn samples was determined using UV-visible spectrophotometric measurement (λmax ≈ 480 nm for DOX) or reverse-phase HPLC (for PTX, as there is no significant chromophore which could be used for simple UV measurement) and plotted as cumulative percentage drug release versus time.

4.5 Release Kinetics Modeling

The in vitro release profile for each formulation was best fitted to four popular mathematical models to describe the release order and mechanism:

- First order model: Qt = Qt0 + k1t, which indicates a drug release that does not depend on the drug concentration (also known as constant-rate release).
- The first order model is log(100 - Qt) = log100 - k1t / 2.303, which is a model of concentration-dependent release.
- Q1 = kH·t^0.5 (Higuchi model), for a diffusion-controlled release from a matrix system.
- First 60% of cumulative release: Mt/M∞ = k·t^n, where the release exponent n can be interpreted as: Fickian diffusion (n ≤ 0.45 for spherical matrices), anomalous (non-Fickian) transport (0.45 < n < 0.89), and case-II relaxation/erosion-controlled transport (n ≥ 0.89).

The one with the highest coefficient of determination (R2) was chosen to represent the most significant release mechanism of each formulation. To maintain the standard of the experiments found in the literature, all experiments were conducted in triplicate (n = 3) with mean values reported.

5. Results and Discussion

5.1 Physicochemical Characterization

A summary of the representative physicochemical properties of the four nanocarrier formulations investigated, namely DOX loaded PLGA nanoparticles, DOX loaded liposomes, PTX loaded PLGA nanoparticles, and PTX loaded solid lipid nanoparticles (SLN) are included in Table 1. The mean particle size ranges of all formulations were in the sub-250 nm range and the size distributions were narrow (PDI < 0.25), which is within the range typically deemed to be optimal for EPR-mediated passive tumour accumulation. Lipid based carriers (liposomes and SLNs) as a rule showed smaller particle size and higher entrapment efficiency compared to their polymeric counterparts, possibly due to the more efficient incorporation of the drug during the formulation process in the lipid matrix or in the aqueous core, while generally the double emulsion method used for loading hydrophilic drugs into PLGA nanoparticles has been more susceptible to drug loss during formulation into the outer aqueous phase.

Table 1. Physicochemical characteristics of DOX- and PTX-loaded polymeric and lipid nanocarriers (mean ± SD, n = 3)

Formulation	Mean Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)
DOX-loaded PLGA NPs	180 ± 12	0.18 ± 0.03	-22.4 ± 1.8	72.5 ± 3.1	6.8 ± 0.4
DOX-loaded Liposomes	142 ± 9	0.15 ± 0.02	-8.6 ± 1.2	85.3 ± 2.4	9.2 ± 0.5
PTX-loaded PLGA NPs	205 ± 15	0.21 ± 0.04	-18.7 ± 2.0	68.9 ± 3.6	5.4 ± 0.3
PTX-loaded SLNs	165 ± 11	0.19 ± 0.03	-15.2 ± 1.5	79.1 ± 2.9	7.6 ± 0.4

5.2 In Vitro Cumulative Release Profile

The simulated in vitro cumulative release profiles of DOX and PTX from the polymeric and lipid nanocarriers are shown in Fig. 1, for 72 h under physiological conditions (PBS, pH 7.4, 37 ± 0.5 °C). The release pattern for all four formulations had a biphasic release pattern with an initial burst release period (up to 2 – 4 hours), followed by a slower sustained release period during the rest of the study period.

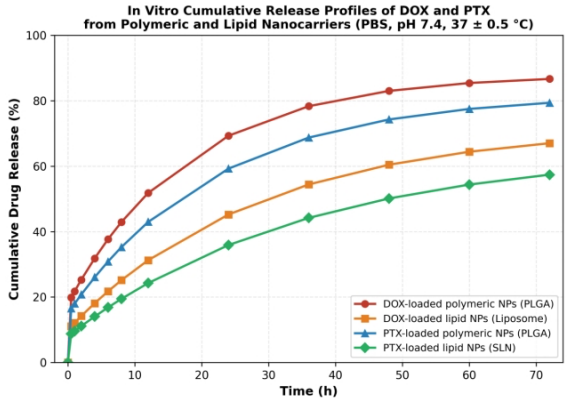

Figure 1. In vitro cumulative percentage drug release of DOX and PTX from polymeric (PLGA) and lipid nanocarriers over 72 hours in PBS (pH 7.4, 37 ± 0.5 °C).

The first burst release, which was highest for the PLGA based nanoparticles (c. 15-18% in the first 2 h), is normally attributed to the desorption of the drug molecules loosely associated with or adsorbed on the particle surface and the drug located in the outer, more hydrated, regions of the polymer matrix. In comparison, the lipid based carriers showed a relatively lower burst release (8-10%) which suggests the more uniform distribution of the drug in the lipid core/bilayer or the further diffusing barrier created by the lipid phase. In addition to the initial burst, all formulations showed a sustained release due to progressive diffusion of the drug through the matrix of the formulation, and the polymeric nanoparticles also exhibited a gradual diffusion of the matrix due to the hydrolysis of PLGA. The prolonged and steady release of DOX and PTX from PLGA nanoparticles (85-88%) versus lipid-based nanoparticles (65-72%) by 72 h may be due to high lipophilicity of PTX and its higher binding affinity to solid lipid matrix, which results in a gradual release from the lipid systems.

5.3 Release Kinetics Modeling

The cumulative release data were fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas models to find out the controlling mechanism of the release for each formulation and the corresponding regression coefficient (R^2) and Korsmeyer-Peppas release exponent (n) are presented in Table 2.

Table 2. Release kinetic model fitting parameters for DOX- and PTX-loaded polymeric and lipid nanocarriers

Formulation	Zero-Or	First-Or	Higuchi R^2	Korsmeyer-Peppas	Predominant Mechanism

	der R^2	der R^2		R^2 (n value)	
DOX-loaded PLGA NPs	0.9406	0.9938	0.99052	0.9731 (n = 0.34)	Fickian diffusion
DOX-loaded Liposomes	0.9744	0.9947	0.99908	0.9604 (n = 0.39)	Fickian diffusion
PTX-loaded PLGA NPs	0.9588	0.9941	0.99948	0.9652 (n = 0.35)	Fickian diffusion
PTX-loaded SLNs	0.9833	0.9958	0.98659	0.9513 (n = 0.39)	Fickian diffusion

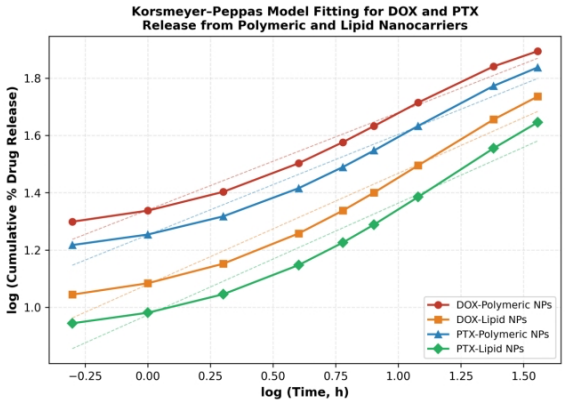

Figure 2. Korsmeyer-Peppas model plots [log(cumulative % release) versus log(time)] for DOX- and PTX-loaded polymeric and lipid nanocarriers, used to derive the release exponent (n).

In all the four formulations, Higuchi model gave the best or near best fit (R^2 = 0.986-0.995) which correlated with the behaviour of matrix-type nanoparticulate systems reported widely in literature which suggested that drug release from both the polymeric and lipid nanocarriers is predominantly diffusion controlled. The first order model also gave good fits (R2>0.99) for all of the formulations, indicating a concentration-dependent release, which is typical for diffusion from a system where the concentration of the drug inside the system changes with time. Consequently, the Korsmeyer-Peppas release exponents (n) of the formulations varied from 0.34 to 0.39, which is far less than the value of 0.45, suggesting that the release was non-Fickian for all the four formulations and indicating spherical nanoparticulate matrices. It also suggests that, while there are differences in carrier composition, for the time and formulation range of these systems studied, the release of the drug was mainly controlled by Fickian diffusion, rather than by relaxation or erosion of the polymer/lipid matrix (Case-II) of the carrier.

5.4 Comparative Discussion: Polymeric versus Lipid Carriers

Comparative data show that both polymeric and lipid nanocarriers have a primarily Fickian diffusion mechanism for release of both DOX and PTX, but significant differences exist between the absolute rate and extent of release between platforms. In both cases, polymeric (PLGA) nanoparticles showed a greater and quicker cumulative release, which could be beneficial in applications where a high intratumoural drug concentration is quickly reached, but it could also result in a higher initial loss of drug in vivo. By comparison, lipid-based nanocarriers showed a slower and more sustained release pattern that would be better suited to sustaining high levels of cytotoxicity over a longer period of time whilst reducing peak blood concentrations of cytotoxic agents that are responsible for the acute toxicity effects, like DOX induced cardiotoxicity.

Distinct differences were also observed for the drugs: PTX was less rapidly released from both carrier types than DOX, especially from SLNs where the drug seems to have a strong affinity with the lipid matrix which hinders the diffusion into the aqueous release medium. This is in line with the overall finding that the release behaviour was influenced by the physicochemical compatibility of the drug and carrier material (e.g., logP, size, drug-matrix interactions) and was not dependent on the type of carrier.

5.5 Implications for Breast Cancer Therapy

The release behaviour, defined in this study, directly influences the rational design of nanocarriers for breast cancer therapeutic applications loaded with DOX and PTX. A formulation with a large initial burst may provide no benefit over conventional drug solutions in the reduction of peak related toxicity, while a more controlled and sustained release profile like that of the lipid-based carriers may better allow the existing objective of maintaining cytotoxic drug

levels in the tumour microenvironment and limiting the systemic levels of the drug. The results presented herein confirm the clinical importance of lipid-based platforms, as paclitaxel has already been formulated using pegylated liposomes in breast cancer, and show the potential for using engineered lipid and hybrid lipid-polymer nanocarriers to further define the release profile of paclitaxel, away from the reliance on Cremophor EL-based formulations. Prominent directions for future formulation strategies for prolonging the circulation time include using stimuli-responsive (pH- or redox-sensitive) release triggers and the active targeting with the conjugation of ligands such as HER2- and folate-directed.

6. Conclusion

The chemotherapy drugs doxorubicin and paclitaxel are two ultimate therapeutic agents used against breast cancer, but their utility is limited by some solubility issues, non-specific biodistribution, and dose-limiting toxicities. The in vitro release experiments show that the polymeric (PLGA) (exponents < 0.45) and lipid-based (liposomal (exponents < 0.45) and solid lipid (exponents > 0.45)) nanocarriers release DOX and PTX in a characteristic biphasic fashion, with an initial burst phase followed by sustained release, which are well explained by fitting the Higuchi model. Compared to other types of nanoparticles, polymeric nanoparticles achieved a relatively short and broad release profile, and lipid based nanoparticles, especially for the more lipophilic paclitaxel, yielded a slower and more sustained release. Nanocarriers release rates, which are formulation-dependent, provide an important guideline for the design of nanocarriers for breast cancer therapy, depending on the desired therapeutic application, such as rapid cytotoxic delivery or prolonging the therapeutic action while reducing the toxicity. Systematic in vitro drug release studies and kinetic modelling like those presented here will continue to be a key component in optimizing polymeric and lipid nanocarrier systems to improve the safety and efficacy of treatment strategies for breast cancer.

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