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A systematic study of temperature sensitive liposomal delivery of doxorubicin using a mathematical model

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ABSTRACT

Background: Temperature-sensitive liposomes (TSL) in combination with hyperthermia (HT) exposure have emerged as a potentially attractive option to achieve therapeutic drug concentration at targeted tumour site while reducing adverse side effects associated with systemic administration of anticancer drugs. The aim of this study is to elucidate the interplay among different kinetic steps by means of computational modelling.

Methods: A multi-compartment model for TSL-mediated delivery of doxorubicin (DOX) is developed, which incorporates descriptions of the pharmacokinetics of TSL and DOX, and their accumulation in tumour tissue following intravascular triggered release. By examining dynamic interactions among TSL properties, tumour physiological properties and treatment regimen, peak intracellular DOX concentration is predicted for continuous and pulse HT exposures.

Results: Drug release rate from TSL has a saturable effect on peak intracellular drug concentration, and no further gain could be achieved for release rates greater than 0.1018 s^{-1}. A similar effect has also been found for heating duration, such that for a given bolus injection, peak intracellular drug concentration reaches its maximum and then levels off after HT duration of 2 h. These results suggest that both TSL release rate and HT duration can be optimised in accordance with other parameters, e.g. clearance rate of TSL and administration mode, in order to achieve a desirable level of intracellular drug concentration. However, prolonged heating is not effective for resistant tumour cells with overexpression of ABC (ATP-binding cassette) transporter proteins.

Conclusions: The results obtained in this study can be used to guide the design and optimisation of TSL parameters and treatment regimens.

1. Introduction

Liposomal encapsulation of anticancer agents, as a drug delivery system, has been developed to overcome the limitations of conventional free drug treatment, by reducing systemic cytotoxicity, prolonging plasma half-life and passively targeting tumour sites as a result of enhanced permeability and retention (EPR) effect [1]. Liposomal formulations of doxorubicin (DOX) (e.g., Doxil®) have been approved for clinical use in the treatment of ovarian cancer; however, their clinical efficacy is limited by insufficient local DOX concentration due to slow release kinetics. Therefore, considerable effort has been made on designing liposomes that are capable of targeting tumour actively and releasing encapsulated agents rapidly in response to specific stimulus, temperature-sensitive liposomes (TSL) being one of these [2].

As a localised therapy, TSL are expected to remain stable at body temperature but can be triggered to release the encapsulated drug rapidly (within seconds to minutes) when they are heated to a designated temperature at the tumour site [3,4]. In addition, local hyperthermia (HT) alone has been shown to improve accumulation of TSL in solid tumour by accentuating the leakiness of tumour vasculature [5]. Among several HT applicators, such as radiofrequency, microwave, and lasers, high intensity focused ultrasound (HIFU) has a distinct advantage due to its non-invasive and controllable nature [2]. More importantly, when combined with magnetic resonance imaging (MRI), MRI guided HIFU can offer real-time temperature monitoring with a feedback control, which is critical to TSL-based delivery systems activated by HIFU [6].

The application of TSL in conjunction with local HT has shown promising prospect both in preclinical studies and in clinical trials. Current TSL research is mainly focused on formulation design, especially with regard to release kinetics in response to HT exposure. However, among the multiple transport steps in a drug delivery process, drug release is an intermediate step that is preceded by the upstream transport (systemic circulation) and followed by the

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downstream transport (transvascular/interstitial and eventually intracellular transport). Furthermore, the target output, i.e. peak intracellular drug concentration, is not only influenced by interactions among these multiple transport steps, but also by the characteristics of HT applicators. It is a formidable task to measure the entire range of drug concentrations as well as a large amount of parameters experimentally. On the other hand, it is beyond our intuitive understanding to appreciate temporal variations of drug concentrations, and their dependence on the constituent parameters. For these reasons, an in silico model can play a key role in gaining insights into the transport processes of TSL in combination with their response to HT exposure. In silico experiments can be carried out as a precursor and supplement to experimental studies, in order to provide guideline for further design and optimisation of TSL drug delivery systems and their combination with various HT applicators.

Based on the concept of multi-compartment model, a number of mathematical models [7–12] have been developed to describe biological transport processes involved in stealth liposomes and TSL. These models have provided various levels of insight into the delivery of liposomal carriers, bioavailability in the tumour tissue, and its correlation to cytotoxic effect. In particular, mathematical models of TSL delivery require tempo-spatial profiles of temperature as input (stimulus) to account for temperature-dependent release kinetics. This can be achieved by assuming a homogeneous distribution of desired temperature in the entire tumour region [10], or by coupling with a bio-heat transfer model. In their recently published computational studies, Gasselhuber et al. [9,13] predicted distributions of temperature and drug concentration in response to two different heating modalities, and their numerical results showed a qualitative agreement with preliminary in vivo data. However, a systematic study with a thorough sensitivity analysis of the input parameters is lacking.

Employing a multi-compartment model together with the assumption of a homogeneous temperature distribution, the present study aims to provide clear-cut information on the interplays among multiple transport steps involved in the the delivery of TSL-encapsulated doxorubicin (DOX). Compared to the mathematical models employed by Gasselhuber et al. [9,10,13], an additional compartment for tumour plasma is introduced in the present study, which allows distinction of TSL in systemic plasma from those in tumour plasma. A systematic study is then performed by contrasting and comparing numerical results in response to continuous and pulse temperature stimuli. A sensitivity analysis is carried out to determine which input parameters have the greatest influence on the peak intracellular drug concentration ($c^T_{i,\,peak}$), and how these parameters affect $c^T_{i,\,peak}$ under continuous and pulse HT exposure.

2. Methods

A multi-compartment model (Fig. 1) is adopted to describe the transport of liposomes and unencapsulated drug following intravenous injection of drug-loaded TSL. The model consists of three high level compartments: systemic plasma, lumped tissue and tumour. The tumour compartment is further divided into three sub-compartments, namely tumour plasma, tumour extravascular extracellular space (EES) and tumour intracellular space. There are eight variables representing drug concentrations in either liposomal or free form in different compartments and the mass conservation equation for each variable incorporates kinetic transfer and reaction processes. A general assumption underlying all compartmental models is homogeneity in each compartment, i.e. a well-mixed system with a uniform temperature and uniform tumour cell density. In the equations described in the subsequent sections, drug concentrations are expressed in micrograms (μg) per mm^3 of the volume of their corresponding compartment.

2.1. Pharmacokinetics of TSL: systemic plasma compartment

Pharmacokinetics of TSL is described by one compartment, i.e. systemic plasma. The volume of the central compartment is set to the volume of systemic plasma (V^B_P), which implies that the latter is consistent with the volume of TSL distribution [7]. Following an intravenous injection, the concentration of TSL in systemic plasma compartment ($c^B_{P\_Lip}$) is determined by

$$V^B_P\frac{dc^B_{P\_Lip}}{dt}=\frac{D}{T_d}*H(T_d-t)-k_{e\_Lip}c^B_{P\_Lip}V^B_P-kr_{37}c^B_{P\_Lip}V^B_P+F^T_{PV}V^T_Pc^T_{P\_Lip}-F^T_{PV}V^T_Pc^B_{P\_Lip} \quad (1)$$

where D is the dose of TSL, and T_d is the infusion duration. The Heaviside term $H(T_d-t)$ describes a constant infusion of TSL during the period of $t=0$ to T_d only. Perfect mixing of TSL is assumed within systemic plasma. TSL are eliminated via body clearance at rate k_{e_Lip}. A first order kinetics with a rate constant of kr_{37} is used to describe the release of DOX in systemic plasma due to instability of TSL at body temperature [10].

For bolus injection, Eq. (1) is reduced to

$$V^B_P\frac{dc^B_{P\_Lip}}{dt}=-k_{e\_Lip}c^B_{P\_Lip}V^B_P-kr_{37}c^B_{P\_Lip}V^B_P+F^T_{PV}V^T_Pc^T_{P\_Lip}-F^T_{PV}V^T_Pc^B_{P\_Lip} \quad (1a)$$

2.2. Pharmacokinetics of free DOX: systemic plasma & tissue compartments

Pharmacokinetics of free DOX is described by a two-compartment model, with one common systemic plasma compartment shared with TSL and the other representing lumped body tissues with significant drug uptake. Free DOX is present in systemic plasma compartment due to instability of TSLs at body temperature and is cleared from the body at rate k_e. Exchange of free DOX between systemic plasma compartment and tissue compartment is described by a bidirectional linear kinetics at transfer rate k_P and k_t, respectively.

$$V^B_P\frac{dc^B_P}{dt}=kr_{37}c^B_{P\_Lip}V^B_P-k_ec^B_PV^B_P-k_Pc^B_PV^B_P+k_tc^B_tV^B_t+F^T_{PV}V^T_Pc^T_P-F^T_{PV}V^T_Pc^B_P \quad (2)$$

The concentration of free DOX in tissue compartment (c^B_t) is described by

$$V^B_t\frac{dc^B_t}{dt}=k_Pc^B_PV^B_P-k_tc^B_tV^B_t \quad (3)$$

2.3. Tumour deposition

2.3.1. Tumour plasma compartment

Tumour plasma compartment is linked to systemic plasma compartment via blood perfusion, which accounts for convective transport ($F^T_{PV}V^T_Pc$) of TSL and free DOX between blood and tumour. Here F^T_{PV} is defined as plasma flow per tumour plasma volume. When tumour is heated to a designated temperature (e.g. 42 °C), rapid release of DOX from TSL is triggered in tumour plasma, which is assumed to follow a linear kinetics at rate kr_{42}. After heating is ceased, the release rate is reduced to the rate at body temperature (kr_{37}). The concentration of TSL in tumour plasma compartment ($c^T_{P\_Lip}$) is described as

$$V^T_P\frac{dc^T_{P\_Lip}}{dt}=F^T_{PV}V^T_Pc^B_{P\_Lip}-F^T_{PV}V^T_Pc^T_{P\_Lip}-H(T_h-t)*kr_{42}c^T_{P_{Lip}}V^T_P$$