Research & Reviews: Journal of Pharmacognosy and Phytochemistry

e-ISSN: 2321-6812
p-ISSN: 2347-2332

NANO CONGRESS 2019 In vitro studies of the release of doxorubicin and other amphiphilic drugs from microgels: Improved mechanistic understanding - Per Hansson-Uppsala University

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Short Communication

Abstract

The release rate of doxorubicin (DOX) from the drug-delivery system (DDS), DC Bead, was studied by2 miniaturized in vitro methods: free-flowing and sample reservoir. The dependencies of the release mechanisms on in vitro system conditions were investigated experimentally and by theoretical modeling.An inverse relationship was found between release rates and bead size, most likely due to the greater total surface area. The release rates correlated positively with temperature, release medium volume, and buffer strength, although the release medium volume had larger effect than the buffer strength. The sample reservoir method generated slower release rates, which described the in vivo release profile more accurately than the free-flowing method. There was no difference between a pH of 6.3 or 7.4 on their lease rate, implying that the slightly acidic tum or microenvironment is less importance for drug release. A positive correlation between stirring rate and release rate for all DDS sizes was observed, which suggests film controlled release. Theoretical modeling highlighted the influence of local equilibrium of protonation, self-aggregation, and bead material interactions of DOX. The theoretical release model might describe the observed larger sensitivity of the release rate to the volume of the release medium compared to buffer strength. A combination of miniaturized in vitro methods and theoreticalmodeling are useful to identify the important parameters and processes for DOX release from a micro gel-based DDS.

Introduction

In vitro investigations of drug release from drug-delivery systems (DDS) are of importance throughout the drug innovation and development process.1However, no standardized in vitro method exists for parenteral systems, and as a consequence, there is adversity of in vitro methods. The in vitro release rate of doxorubicin (DOX) from the microsphere DDS, DC Bead, has been investigated in paddle, sample and separate, flow through, and T-cell methods. These in vitro methods use relatively large amounts of DDS (1 mL) and release medium (200-900 ml). Miniaturized in vitro methods reduce the amounts of DDS sample, release medium and waste for example, to 20-65mL (DDS sample) and 10-20 mL (release medium). Another advantage of the miniaturized method is that a low volume of release medium may be more relevant to the in vivo site in hydrodynamic and diffusion properties.In this report, the in vitro release of DOX from the beads was tested in 2 miniaturized methods. The beads were loaded with DOX, a cytotoxic agent that is used in palliative treatment of intermediate-stage hepatocellular carcinoma. DOX has a molecular mass of 543.52 g/mol and a LogD7.5of2.42. The pK as of DOX are 7.34, 8.46, and 9.46, and the compound exists as both a deprotonated and protonated monovalent cation at physiological conditions. The beads consist of polyvinyl alcohol (PVA) with integrated, negatively charged 2-acrylamido-2-methylpropanesulfonate (AMPS) units. Ion exchange has been proposed as the mechanism for loading and release of protonated DOX from the AMPS sulfonic acid groups. The beads are no biodegradable, and the intrahepatic administration leads to a local drug delivery in combination with a full and permanent embolization of the treated hepatic arteries. In the clinic, the beads are delivered by radiological image guidance with anon ionic contrast medium, such as Omnipaque. The main objective of this study was to determine the mechanism(s) and release rate of DOX from the beads. Second, we investigated the effects of factors such as temperature, stir-ring rates, buffer strength, pH, and volume of release medium on the in vitro release rate. Third, selected in vitro release profileswere compared to an in vivo DOX-release data set. Finally, the release mechanism(s) were investigated with theoretical modeling.

Experimental

Design Am Diss profiler (pION) was used to determine the in vitro DOX release from the beads during various conditions. The drug concentration in the medium was determined as the area under the concentration wavelength curve of

Note: This work is partly presented at 31st Nano Congress for Future Advancements August 29-30, 2019 | London, UK

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p-ISSN: 2347-2332

the second derivate spectrum at an interval of 553 to 572 nm. The application of the second derivate spectrum reduces the background turbidity, thereby enhancing peaks and reducing baseline shifting.21, 22Each channel was individually calibrated with the stock solutions against a standard curve. All release studies were per-formed under sink conditions (amount of DOX <10% of the solubility), in 3 or more replicates, and the samples were protected from light with tinfoil during the experiments. The temperature was kept constant during the release experiments using a water bath

In Vitro Release of DOX From Beads in Free-Flowing Method The free-flowing in vitro setup is shown in Figure 1a. For each experiment, 55mL of beads was transferred into a glass vial containing 20 mL of buffer I, at 37 °C. The in vitro drug release of DOX from each of the 3 bead sizes was investigated at stirring rates of 0,100, and 400 rpm. A Teflon-coated magnet for stirring was used throughout the experiment

In Vitro Release of DOX From Beads in the Sample Reservoir Method A modified sample reservoir (SR) method (adapted from the study by Unfelt et al.10) is illustrated in Figure 1b. Discs with diameter of 22 mm were manufactured (Loostec AB, Loos, Sweden)in polyether ether ketone (PEEK) with a magnet (3.5 ⌐15 mm),embedded inside the disc. The discs were manufactured with 2different cylindrical cavities. SR 6 had a diameter of6 mm, a depth of2 mm, and a cavity volume of 57mL; SR 8 had a diameter of 8 mm, adept of 1 mm, and a cavity volume of 50mL. To avoid formation of air bubbles, the cavity of SRs 6 and 8 was overloaded with 60mLor65mL,respectively, of each bead size. A nylon mesh filter (Merck Millipore Ltd, Darmstadt, Germany) with a pore size of 80mm was soaked in deionized water for 10 min at room temperature before use to retain he beads in the SR. A PEEK plate was placed on top of the mesh filter, and a PEEK lid was used to assemble the sample holder. Two inte-grated wings (5.5 ⌐1⌐2 mm) in the lid stirred the release medium. Unless otherwise stated, 20 mL of buffer I, at 37 °C and a stirring rate of 400 rpm, was used throughout the experiment. In addition, the DOX transport across the nylon mesh was examined with an aqueous solution of DOX (2 mg/mL) in the 6-mm SR

Conclusion:

Smaller beads (70-150mm) have up to twice there lease rates of larger beads (100-300 and 300-500mm), indicating the crucial role of the available total surface area for drug release. The temperature-dependent in vitro release demonstrated the impact of viscosity and diffusion constant changes. Buffer strengths of 10 mm decreased the released amount (Amax) of DOX with70%-80% compared 100 mm This is explainable, to some extent, by the corresponding decrease of positively charged ions. The combination of the 6-mm SR and 10-15 mL release medium described the in vivo release most accurately. The in vitro release of DOX was not influenced by pH, which indicates that the pH in the tumor microenvironment would not much affect the drug release of DOX from the beads in vivo. However, the influence of electrolytes on the in vivo release remains to be investigated. The release mechanism in the free-flowing method was film control, which was confirmed by the positive correlation between release rate and stirring rate for all bead sizes. The theoretical release modelling also suggested that the release of DOX from the beads was influenced by DOX-DOX aggregates, DOX-PVA interactions, and the equilibrium between protonated and deprotonated DOX. In addition, the available volume of release medium, potentially affecting the hydrodynamics and diffusion at the target site, may have had a greater impact on the release of DOX than that of the buffer strength. In future work, we intend to implement a thermodynamic model with a model for the release kinetics. This thermodynamic model will include charge regulation effects and aggregation in the solution, as well as the actual volume change of the beads.

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