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PBPK Modelling for Intratumoral Biodistribution of Magnetic Iron Oxide Nanoparticles

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Extended Abstract

Iron oxide nanoparticles (NPs), particularly magnetic iron oxide (MIO) nanoparticles, may provide a potential therapeutic intervention in therapy, due to their ability to induce hyperthermia at sites in which they accumulate, such as solid mass tumours. Cancer cells respond significantly to the elevated temperature (hyperthermia) initiated by MIO, causing their shrinkage and death. However, it is essential to characterise MIO distribution and retention locally in the tumour mass after interstitial/intratumoral injection to more fully understand key aspects of their efficacy and safety profile. There is a paucity of studies that have fully elucidated dose-response profiles for MIO owing to the complexity of solid tumour physiology and MIO biodistribution characterisation locally, within the tumour. The work described here, has developed a novel mechanistic, and physiologically based pharmacokinetic (m-PBPK), model to predict the distribution and retention of MIO NPs within the tumour.

The PBPK murine model was used to simulate tumour bearing mice connected with whole-body tissues. A pancreatic solid tumour mass was integrated as a 3-D sphere composed of three tumoral sub-compartmental regions: proliferative, quiescent and necrotic. The simulated tumour volume ranged between 200-2000 mm^3, designed in Simbiology v. 9.6.0 (MATLAB R2019a). Each sub-compartment representing the main components of the tumour microenvironment resemble the interstitial space where tumour-associated macrophages and tumour cells are bathing. The primary process underpinning MIO distribution in the tumour is interstitial fluid flow (IFF). IFF drives MIO movement from one layer to another, represented using first-order kinetics equations. To date, IFF is influenced extensively by tumour type and tumour size, considering their high variability between tumours. The model was validated using preclinical pancreatic tumour mice computerised tomography (CT) data on interstitially administered MIO NPs (1.8 $mg_{MIO}/100\ mm^3_{Tumour}$).

Median predicted amount (A_{median}) of MIO retained within the tumour (tumour volume = 204 mm^3) after 2 hours was 3.2 ± 0.20 mg (87%) compared to the observed 3.3 ± 0.19 mg (89%). For further validation, the absolute average fold error (AAFE) estimated that the predicted A_{median} was below 2-fold of the observed A_{median} = 1.015. Additionally, simulations predicted a semi-quantitative gradual distribution of MIO within the tumour mass, but most particles concentrated at the injection site (the necrotic sub-compartment layer) as also observed from the preclinical CT data and in literature.

The m-PBPK model successfully provided valuable estimates of MIO retention in the tumour in addition to their local distribution within tumour from the site of injection. Further optimisation of the m-PBPK approach with integration of experimental *in vitro* data, such as macrophage uptake and release, would be beneficial to improve quantitative pharmacokinetic predictions.

Keywords: Iron oxide, nanoparticle, tumour, PBPK and biodistribution.