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METHOTREXATE pH-RESPONSIVE RELEASE FROM NANOSTRUCTURES OF DOPAMINE AND POLYOXOMETALATE

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ABSTRACT : The synthesis of nanostructure of dopamine (D) and phosphotungstic acid (PWA) loaded with methtrexate (MTX) via self-assembly of the organic–inorganic hybrid D and PWA is described. The amount of MTX drug loaded in nanostructure of PWA-D was determined using UV/Vis spectroscopy and found to be about 3% (by weight). The as-prepared rice-like nanostructure of PWA-D loaded with MTX showed promising pH-dependent release behaviour, suggesting that a nanostructure of PWA-D is a good candidate for the oral delivery of MTX in the chemotherapy. The release behaviour of the as-prepared rice-like nanostructure of PWA-D loaded with MTX at pH 7.4 showed a higher release profile than at pH 2.8. The morphology of the as-prepared nanostructures wasdeterminedvia SEM-EDX measurements.

Key words : Methtrexate, polyoxometalate, pH-dependent release, nanostructures, drug delivery.

INTRODUCTION

Methotrexate (MTX) is a folate antagonist drug, which is widely used in the treatment of Crohn's disease, cancer, rheumatoid arthritis and psoriasis (Cutolo, 2001; Reich *et al*, 2012). MTX has been used as the primary systemically administered drug for the treatment of severe psoriasis for over 25 years. MTX is a cell cycle phase-specific drug that only kills cancer cells when they are dividing and has been used for nearly 40 years as an antimetabolite for cancer therapy, dermatology, rheumatology and penology (Eichholtz and Trott, 1980; Lange *et al*, 2016; Busger Op Vollenbroek, Doggen *et al*, 2018). However, MTX is rapidly cleared from the in cerebrospinal fluid (CSF); therefore, repeated intrathecal or intraventricular injections have to be used to maintain a sustained cytotoxic drug concentration (Shapiro *et al*, 1975; Bleyer *et al*, 1978). Moreover, MTX sometimes causes side effects such as nausea, vomiting, stomach pain, drowsiness, or dizziness, and also temporary hair loss due to the rapid destruction of cancer cells (tumour lysis syndrome) (Akýncý *et al*, 2018; Giletti and Esperon, 2018; Wolmarans *et al*, 2018). MTX has a high solubility and low permeability and hence is classified as a class III drug in the Biopharmaceutical Classification System. Its low permeability and low oral bioavailability are due to the action of the P-glycoprotein (P-gp) as an efflux pump limits MTX use when the therapy requires systemic absorption (Huber *et al*, 2010). An excess of drug is usually administered to overcome these limitations, but the side effects are thus amplified (Barrueco *et al*, 1992). Hence, new controlled-release strategies for MTX are needed to maintain therapeutic drug concentrations in the CSF for an extended period and to overcome these problems. This can be achieved via the utilization of nanotechnology as a tool toenable the building of new nanostructures with variedand improved properties. Nanostructures have attracted considerable attention in recent years, because of their unique characteristics as well as the number of potential applications including electronic, magnetic, optoelectronic and catalytic to biomedical (Zhang *et al*, 2017; Jeevanandam *et al*, 2018). Among other building blocks, polyoxometalates (POMs) have attracted considerable attention as suitable inorganic building blocks and often used for designing of hybrid materials due to their numerous electronic, magnetic, photochemical, biomedical and catalytic properties (Rhule *et al*, 1998, Al-Yasari and Fielden, 2014). POMs are well-known anionic metaloxygen nanoclusters whose sizes andshapes are amenable to control, and are highly negatively charged structures (Gumerova and Rompel, 2018). Li *et al* (2014) have reported the self-assembly of D and polyoxometalate; PWA resulting in a hierarchical nanostructures form for the oral drug delivery of Doxorubicin.