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Thermally reactive *N*-(2-hydroxypropyl)methacrylamide (HPMA) amphiphiles for drug solubilisation

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ABSTRACT

Thermally active polymers, can respond structurally to temperature changes, making them interesting as potential drug delivery vehicles. Polymers of *N*-(3-aminopropyl) methacrylamide hydrochloride (APMA) are cationic with primary amine groups in their structure, which have been explored in biomedical applications via post-polymerisation modifications. In this work, we synthesised amphiphilic APMA monomers using hydrophobic pendant groups via conjugation onto their primary amine group. The pendant groups chosen in this study were palmitoyl, dansyl and cholesteryl moieties. The amphiphilic monomers were subsequently copolymerized with *N*-(2-hydroxypropyl)methacrylamide (HPMA) using varied monomer feed ratios resulting in a thermo-responsive system. The ability of the resultant aggregates in aqueous solution to encapsulate and liberate model drugs (e.g., propofol, griseofulvin and prednisolone) was then determined. Our data showed that the HPMA based formulations were capable of loading the model drug molecules inside their lipophilic core; HPMA-co-(APMA-Dansyl 2%) exhibited the largest drug encapsulation ability. Subsequently, poly(ethylene glycol) (PEG) was incorporated into the intrinsic polymer structure. This resulted in a more rapid drug release profile, whereby 100% of griseofulvin and prednisolone were liberated after only 4 h, which was only 5% and 10% before the PEG inclusion, respectively. Similarly, propofol showed 70% liberation from the polymer aggregate after 24 h, compared with only 30% liberation pre-PEGylation. These studies give an insight into the potential of the HMPA based amphiphiles as thermally responsive cargo carrier/release systems which could be exploited in the delivery of poorly soluble drugs.

1. Introduction

Thermally active polymers have attracted great attention for their potential in the area of drug delivery. They are classed by their lower critical solution temperature (LCST) or upper critical solution temperature (UCST) properties. Relevant specifically for drug delivery, those polymers that exhibit structural changes or deformation at their LCST are of interest. These structural changes lead to the ability to change polymer solubility in aqueous environments (Taskeen et al., 2020). Such deformation could help to overcome the challenges faced currently in the delivery of compounds to site of need, such as in cancer chemotherapy where highly potent compounds cause great physiological detriment when circulated systemically, often hindering their dose threshold and use.

Some of the most successful thermally active polymeric drug delivery systems are based on the use of poly(*N*-(2-hydroxypropyl) methacrylamide) (HPMA) polymers and their derivatives (Bobde et al., 2020; Talelli et al., 2010; Das et al., 2020; Alsuraifi et al., 2018; Ellah et al., 2015; Johnson et al., 2011). HPMA is non-immunogenic, biocompatible, allows the possibility of functionalization and acts in a thermo-responsive manner (Talelli et al., 2010). *N*-(3-aminopropyl)methacrylamide (APMA) is a monomer, which possesses a primary amine group in its structure. In the literature, APMA is reported in the fabrication of polymers and their associated nano-aggregates, which have been used for the delivery of drug compounds and genes (Mendonça et al., 2014). APMA is easily tailored for applications via modification of the primary amine residue in its structure, enabling the possible conjugation of a host of hydrophobic groups. Chu and colleagues

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