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Introducing a highly dispersed reduced graphene oxide nano-biohybrid employing chitosan/hydroxyethyl cellulose for controlled drug delivery

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ABSTRACT

In this research, an attempt was made to stabilize reduced graphene oxide (rGO) in all pH ranges, incorporating both chitosan (CS) and hydroxyethyl cellulose (HEC) to make a proper drug carrier with suitable stability and drug release behaviour. The stability of rGO-CS-HEC nanohybrid was assessed using field emission scanning electron microscopy (FE-SEM), ultraviolet-visible spectroscopy (UV–Vis) and Zeta potential measurements. Results depicted that the novel synthesized nanohybrid was stable in all pH ranges, due to the utilization of HEC, while without incorporation of this material, the rGO-CS nanohybrid aggregated at neutral and alkaline media, due to the ionic nature of chitosan. In addition, drug loading and release behaviour of folic acid (FA), as a model drug, was investigated to assess the role of chitosan on the release behaviour of FA from the rGO-CS-HEC nanohybrid in comparison with rGO-HEC and rGO-CS nanohybrids. It was proved that the resultant nanohybrid could release nearly 27% more FA than the rGO-HEC nanohybrid and only 9% lower than the rGO-CS nanohybrid during 120 h. Moreover, the biocompatibility of the resultant nanohybrid was also checked to introduce the novel rGO-CS-HEC nanohybrid as a suitable candidate for drug delivery application.

1. Introduction

Graphene oxide with its two-dimensional structure has shown potential applications in the field of targeted drug delivery (Mo et al., 2015; Shi et al., 2013; Wang et al., 2013; Wei et al., 2016; Xie et al., 2016; Yang et al., 2016; Zheng et al., 2015). This nanomaterial with its planar structure is capable of immobilizing different drug molecules, hydrophilic and hydrophobic, by non-covalent bonding or π-π interaction with high loading capacity, and it can respond to different stimuli for drug release (Hu et al., 2012; Rana et al., 2011; Yang et al., 2008; Zhang et al., 2011). However, the aggregation of GO in electrolyte solutions, such as blood media, restricts its effectiveness for drug delivery application (Hong et al., 2011; Wang and Hu, 2013). Therefore, stabilization of GO suspension in electrolyte media is the most important challenge for any biological application of this injectable drug carrier.

In this regard, functionalization of GO with different water soluble and biocompatible polymers has been practiced to stabilize GO in electrolyte solutions for various biological applications(Bao et al., 2011; Hu et al., 2012; Lee et al., 2011; Liu et al., 2008; Rana et al., 2011). For instance, chitosan (CS) as an ionic biopolymer, has been widely used for stabilization of GO in acidic media to form an effective pH-responsive drug carrier for cancer therapy (Ardeshirzadeh et al., 2015; Duran et al., 2015; Justin and Chen, 2014; Park et al., 2010). However, in contrary to high release rate and pH-responsivity of GO-CS nanohybrid, it starts to be aggregate in neutral and alkaline solutions (Fang et al., 2010; Liu et al., 2012), such as blood media and normal cells, due to the deprotonation of

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chitosan's amino groups (Afshari et al., 2015). This aggregation severely affects the utility of the nanohybrid as a drug carrier, because the nanohybrid must be stable when it passes through the blood media to show the maximum effectiveness and evade the reticuloendothelial system (RES). Therefore, the stabilization of GO-CS nanohybrid in all pH ranges is crucial for its application as a drug carrier for cancer therapy, although in many researches, less attention has been paid to this important point, and the stability of the nanohybrid has been assessed only in acidic media, unlike the importance of colloidal stability in all pH ranges for drug delivery systems.

In our previous study (Mianehrow et al., 2015), hydroxyethyl cellulose (HEC), a water soluble, non-ionic derivative of cellulose, was utilized as GO stabilizer for drug delivery application and the resultant nanohybrid presented high and long term stability in different electrolyte media, independent of the ionic nature of the

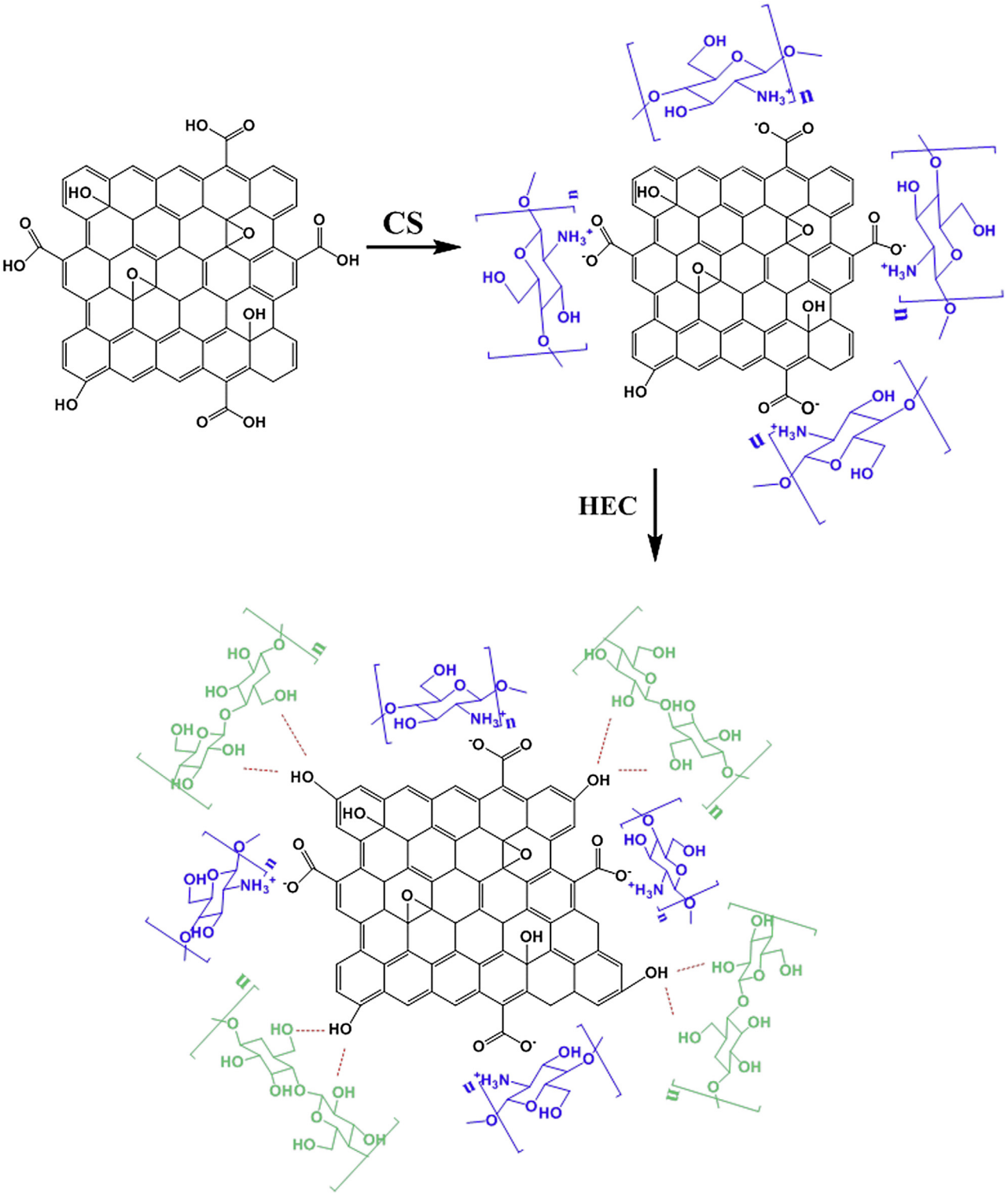

Fig. 1. Schematic of rGO-CS-HEC nanohybrid synthesis.