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Synthesis and characterization of silane coated magnetic nanoparticles/ glycidylmethacrylate-grafted-maleated cyclodextrin composite hydrogel as a drug carrier for the controlled delivery of 5-fluorouracil

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ABSTRACT

A novel drug delivery system (DDS), 3-methacryloxypropyl trimethoxy silane coated magnetic nanoparticles polymerized with glycidylmethacrylate-grafted-maleated cyclodextrin (MPTMS-MNP-poly-(GMA-g-MACD)) was prepared in the presence of ethyleneglycoldimethacrylate as cross-linker and a,a′-azobisisobutyronitrile as initiator and characterized by means of SEM, FT-IR, XRD, DLS, VSM and TEM. The encapsulation efficiency (EE) and drug loading efficiency (DLE) of the DDS were tested using various formulations of DDS. The DDS showed activity against gram positive and negative bacteria. The cytotoxicity studies were also performed using MCF-7 (human breast carcinoma) cells and found that the drug carrier is biocompatible and it shows sustained and controlled release of drug to the targeted site. The drug release mechanism was found to obey non-Fickian diffusion ($n = 0.709$) method where polymer relaxation and drug diffusion played important roles in drug release. In this DDS, advantages of core magnetic nanoparticles and host–guest interactions of β-CD were combined for the controlled delivery of 5-Fluorouracil (5-FU) to maintain the therapeutic index of the drug.

1. Introduction

5-Fluorouracil (5-FU), a hydrophobic drug showing broad spectrum activity against solid tumors of stomach, colon, lung and breast, belongs to the group of antimetabolite of the pyrimidine analogue [1]. The exposure of normal cells to therapeutically effective concentrations of the drug is a major limiting factor for the use of cytotoxic drug and it causes disorders of the bone marrow and the epithelium of the gastro-intestinal tract, which limits its therapeutic effect. So in order to minimize the toxic side effects and the delivery problems, a suitable drug delivery system (DDS) is needed for the controlled administration of 5-FU [2]. Design of DDS with biocompatibility and biodegradability is of great interest during the past decades because it ensures the long term safety of the drugs [3]. The DDS based on magnetic nanoparticles as core was proposed in the late 1970s [4]. The DDS based on metallic nanoparticles is a cost effective DDS because of the simplicity and stability, high efficacy and target identification, ease of circulation and most importantly it is easy to manipulate from synthesis to disposal [5]. Usually to minimize the high chemical activity and oxidizing power of naked metallic nanoparticles, several strategies like grafting or coating with organic species (surfactants or polymers) or inorganic layers (silica/carbon) are developed. This grafting or coating can be utilized for further functionalization of the surface of polymers which enables effective interaction between the DDS and the therapeutic drug so that targeted chemotherapy with minimal adverse effects of the drug is possible [6]. Silanes have been studied as a covalent anchor group suitable for modifying iron-oxide nanoparticles. Stanislav et al. [7] prepared and studied the different properties of 3-aminopropyltriethoxysilane coated iron oxide nanoparticles. Deepthy et al. [8] studied 3-aminopropyltriethoxysilane coated magnetic nanoparticles coupled with glutaraldehyde for the immobilization of esterases from pseudozyma sp. NII 08165 and found that the MNP immobilized esterases had prolonged shelf life and there was no loss in enzyme activity. In the present work, we have coated magnetic nanoparticles (MNPs) with 3-methacryloxypropyltrimethoxy silane (MPTMS) having vinylic functionality so that other vinylic monomers can be introduced on its surface through radical polymerization.

β-cyclodextrin (β-CD), a cyclic oligosaccharide, has been widely explored for affinity based drug delivery. Its hydrophobic core is used for encapsulating small hydrophobic molecules and thus changing the properties of the drug such as aqueous solubility, stability and bioavailability. Also this reduces the side effects of the drug like gastrointestinal

Abbreviations: DDS, Drug delivery system; EE, Encapsulation Efficiency; DLE, Drug loading efficiency; FT-IR, Fourier transform infrared spectroscopy; XRD, X-ray diffraction; SEM, Scanning electron microscopy; DLS, Diffuse light scattering; β-CD, β-cyclodextrin; 5-FU, 5-Fluorouracil; DMF, Dimethyl formamide; MNP, Magnetic nanoparticles; MPTMS, 3-methacryloxypropyltrimethoxy silane; MAH, Maleic anhydride; MACD, Maleated cyclodextrin; GMA, Glycidylmethacrylate; AIBN, a,a′-azobisisobutyronitrile; EGDMA, Ethyleneglycoldimethacrylate; PBS, Phosphate buffer solution; MTT assay, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide; DMEM, Dulbecco's modified minimal essential media; FCS, Fetal calf serum; M_s, Saturation magnetization values.

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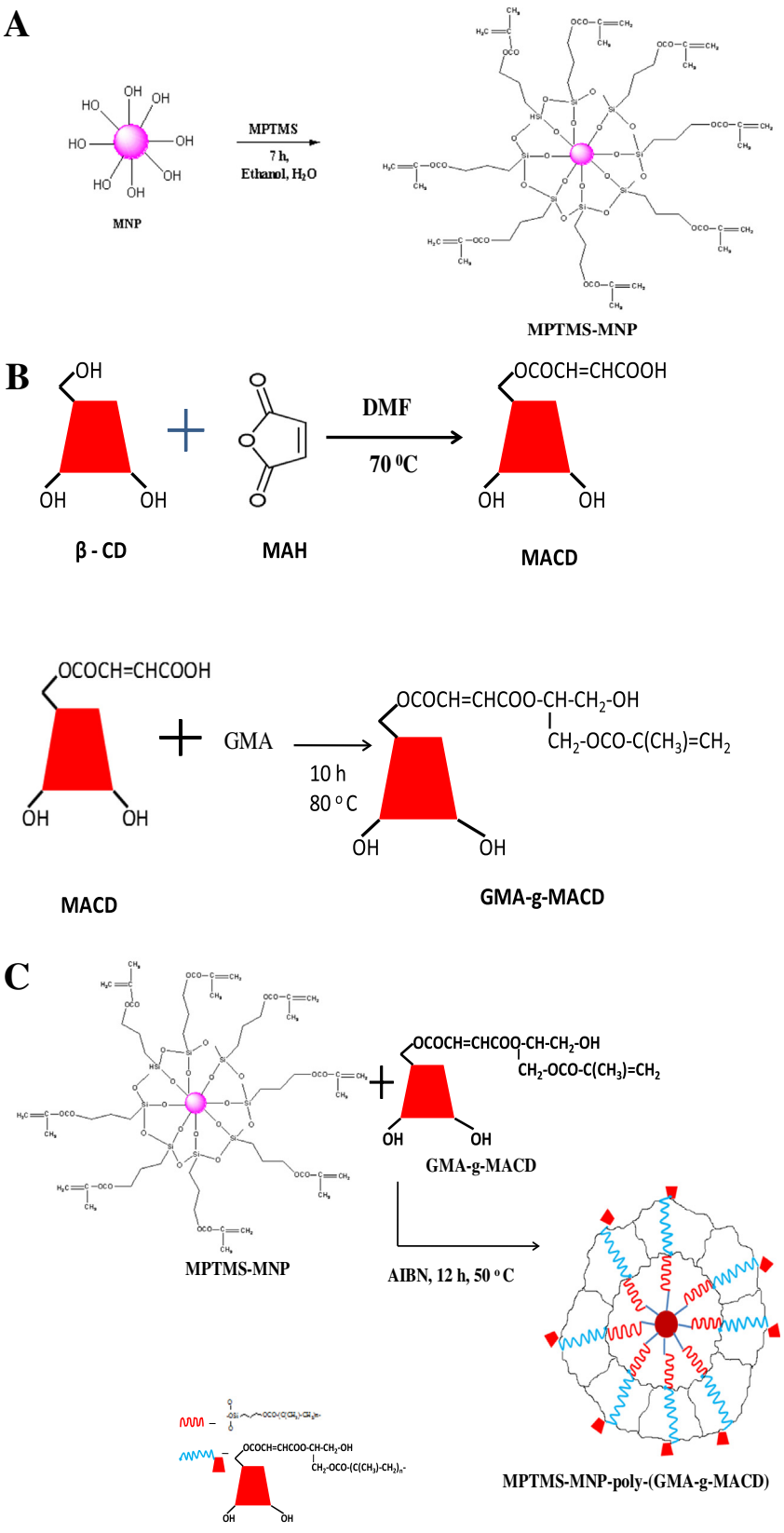
or ocular irritations, and unpleasant taste and smell. Although β-CD has biodegradable properties, it has several adverse effects like nephrotoxicity and low aqueous solubility. So the modification of parent β-CD is needed for its application in bio-medical field. Grafting of β-CD with maleic anhydride (MAH) produces a new material, maleated cyclodextrin (MACD) with interesting properties such as water solubility, less toxicity and pH sensitivity [9,10]. Further modification of MACD with glycidylmethacrylate (GMA) increases the biocompatibility; moreover,



Scheme 1. Preparation of MPTMS-MNP-poly-(GMA-g-MACD).