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# Polymer grafted-magnetic halloysite nanotube for controlled and sustained release of cationic drug

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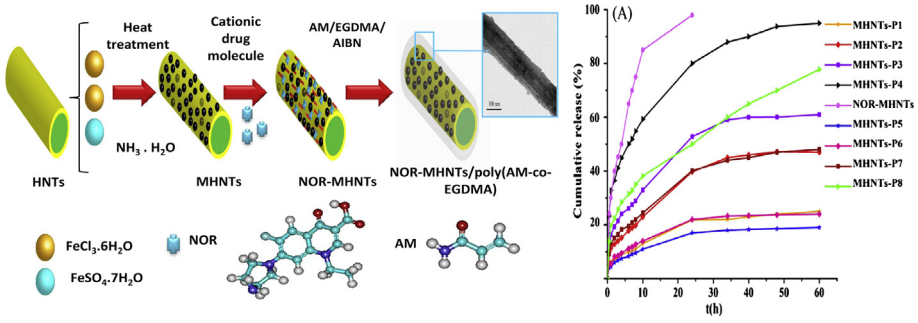
## GRAPHICAL ABSTRACT

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## ABSTRACT

In this research, novel polymer grafted-magnetic halloysite nanotubes with norfloxacin loaded (NOR-MHNTs) and controlled-release, was achieved by surface-initiated precipitation polymerization. The magnetic halloysite nanotubes exhibited better adsorption of NOR (72.10 mg $g^{-1}$) compared with the pristine HNTs (30.80 mg $g^{-1}$). Various parameters influencing the drug adsorption of the MHNTs for NOR were studied. Polymer grafted NOR-MHNTs has been designed using flexible docking in computer simulation to choose optimal monomers. NOR-MHNTs/poly (methacrylic acid or acrylamide-*co*-ethylene glycol dimethacrylate) nanocomposite were synthesized using NOR-MHNTs, methacrylic acid (MAA) or acrylamide (AM), ethylene glycol dimethacrylate (EGDMA) and AIBN as nanotemplate, monomers, cross linker and initiator, respectively. The magnetic nanocomposites were characterized by FTIR, TEM, XRD and VSM. The magnetic nanocomposites show superparamagnetic property and fast magnetic response (12.09 emu $g^{-1}$). The copolymerization of monomers and cross linker led to a better sustained release of norfloxacin ( >60 h) due to the strong interaction formed between monomers and this cationic drug. The cumulative release rate of NOR is closely related to the cross linker amount. In conclusion, combining the advantages of the high adsorption capacity and magnetic proprieties of this biocompatible clay nanotube and the advantages of polymer shell in the enhancement of controlled-sustained release of cationic drug, a novel formulation for the sustained-controlled release of bioactive agents is developed and may have considerable potential application in targeting drug delivery system.



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## 1. Introduction

In recent years nanoscale controlled drug delivery systems allowed for essential progress in pharmaceuticals [1,2]. Drug carriers were employed to improve therapeutic efficacy, inefficient amounts and minimize the adverse side effects that may occur depending on dosage forms [3]. Green nanotechnology aims at developing environment safe and less harmful nano products [4]. Nowadays, a lot of nanomaterials have been utilized in medical science and clinical chemistry. But, controlled synthesis of nanomaterials, loading efficiency, biocompatibility, special release properties and economical efficiency have always been regard as limits in this field. Among different types of nanostructures, nanoclays with excellent properties have shown potential in the field of controlled release of drug molecules [5], including small molecules [6], DNA [7], and Proteins [8]. Carbon nanotubes (CNTs) were also investigated as potential delivery vehicles of nucleic acids, proteins and drug molecules, as well as ceramic nanotubes, including $TiO_2$, $ZrO_2$, $CeO_2$, and $ZnCr_2O_4$ [9,10]. However, toxicity concerns and high cost make these materials less attractive for large-scale applications [11,12]. Therefore, to find novel tubular nanomaterials for drug release is highly desired.

Halloysite nanotubes (HNTs) are clay aluminosilicate mineral. Their deposits are found in China, Australia, USA, New Zeland, Brazil and France [13]. They are chemically similar to the structure of kaolinite, and have a molecular formula of $Al_2Si_2O_5(OH)_4{\cdot}nH_2O$ The HNTs range in length from 500 to 1000 nm; the inner diameter and the outer diameter of the tubes range from 10 to 100 nm and 30 to 190 nm, respectively [14]. Due to a small number of hydroxyl groups on its surface, halloysite has exclusive properties. The majority of the external morphology of HNT consists of siloxane groups (Si—O—Si); whereas, there are many functional groups (hydroxyl group, Al—OH) lining the internal surface of HNT [15,16]. Due to their special hollow tubular structure, excellent properties, plentiful resources and low cost, various exciting applications have been proposed for these nanomaterials. For instance, analytical application which was used as sorbent for solid phase extraction [17–20], electrochemical sensing [21] and biomedical application include their use as gene delivery systems, cancer cell isolation, stem cell isolation, tissue engineering, cosmetic and controlled drug delivery [5,22–25] which is attracting a growing scientific interest in these years. In the field of nanoscales, both HNTs and CNTs are proving to be ideal candidates for new drug delivery system [26,27]. Both nanomaterials possess advantages and disadvantages for drug delivery. Compare to CNTs, HNTs have a larger lumenal diameter and can be loaded with heavier biomolecules. Besides, HNTs are biocompatible, at least at low rage [28–31]. In vitro cell toxicity tests using human dermal fibroblasts and breast cells revealed that HNTs were non-toxic to the cells and even much less toxic than usual salt [32]; While CNTs have been proved to be poisonous. The main advantage of CNTs over HNTs is the vast amount of publications regarding to their properties and potential uses in nanomedicine. However, the cheap price is still able to make HNTs powerful competitor to CNTs [25,32].

In the controlled delivery system the first studies on the release behavior of HNTs showed that release rate of Khellin, tetracycline HCl, and nicotinamide are diminished 10–20 times in comparison with the pure drug crystals [33]. The modification of HNT surfaces for the controlled release rate was attracted great attention of many researchers these years. The control of drug loading and release has been achieved by various methods [34], including silanization of lumen for inner tube [35], formation of organized polyelectrolyte nanoshells with layer-by-layer (LBL) self-assembly [36–38], modification of multilayer films [39], preparation of magnetic microspheres for the sustained-release drug delivery system of ofloxacin [40], hydrophobic modification on the external surface using tetraethoxysilane (TEOS) and octyltriethoxysilane (OTES) [41], Coating with Chitosan polysaccharide [42] and grafting of pH-responsive PDMAEMA chains at the surface of HNT [43]. Previous applications have theoretically and experimentally profited from the fact that HNTs possess good biocompatibility and easy modification. Different chemical constitutions determine the negatively charged outer surface and positively charged inner lumen within a certain pH range (between 3 and 10) [44,45]. Recently, halloysite nanotubes have been used in the nanoscale drug delivery systems of opioid fentanyl [46], tetracycline [47], ibuprofen [48], metronidazole [49], diclofenac sodium [39] and ofloxacin [22,24], which all focused on its inherent lumen. Inspired by preliminary work, we focused our present studies on the preparation of a novel magnetic clay nanotubes grafted polymer using vinyl monomers. The polymers developed from these monomers have been reported as non-toxic and have been used to develop the sustained-release drug delivery system. Moreover, in order to avoid the decreasing in the loading capacity of the drug on the grafted polymer onto the surface of HNTs [43]. In this work, the drug was adsorbed first on the surface of nanotubes and then the grafting of polymer by surface-initiated precipitation polymerization on the drug loaded halloysite nanotubes was carried out. To study the interaction between nanotemplate-monomer complexes, flexible docking method was successfully used in computer simulation and four representative monomers were chosen for this investigation, methacrylic acid (MAA), acrylic acid (AA), acrylamide (AM) and methacrylamide (MAM). NOR-MHNTs/poly (methacrylic acid-*co*-ethylene glycol dimethacrylate) and NOR-MHNTs/poly (acrylamide-*co*-ethylene glycol dimethacrylate) were synthesized using NOR-MHNTs as nanotemplate, acrylamide or methacrylic acid as monomer (AM or MAA), ethylene glycol dimethacrylate (EGDMA) as cross linker and azobisisobutyronitrile (AIBN) as initiator. The mechanism of drug uptake on magnetic halloysite was elucidated and the controlled release of NOR as cationic model drug from NOR-MHNTs/poly (MAA-*co*-EGDMA) and NOR-MHNTs/poly (AM-*co*-EGDMA) is studied. An adsorption of the cationic drug on the surface of biocompatible magnetic clay nanotube coupled with the polymer shell formation provides a novel formulation for the controlled release of cationic bioactive agents.

## 2. Experimental

### 2.1. Materials

Halloysite clay was supplied from DanjiangKou, China. Norfloxacin, Ethylene glycol dimethacrylate (EGDMA), methacrylic acid (MAA) and acylamide (AM) were obtained from Aladdin Industrial Corporation (Shanghai, China). Ferric chloride hexahydrate ($Fe^{3+}$) and dimethyl sulfoxide (DMSO) were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Ferrous sulfate heptahydrate ($Fe^{2+}$), ammonium hydroxide ($NH_3{\cdot}H_2O$) and acetic acid were obtained from Nanjing Chemical Reagent Co., Ltd (Nanjing, China). All chemicals and solutions used were of analytical reagent grade.

### 2.2. Computer simulation

The drug Norfloxacin and four representative monomers (methacrylic acid (MAA), acrylic acid (AA), methacrylamide (MAM) and acrylamide (AM)) were constructed and minimized using force field parameter Merck Molecular Force field (MMFF94X) implemented in Molecular Operating Environment