Mechanically robust dual responsive water dispersible-graphene based conductive elastomeric hydrogel for tunable pulsatile drug release

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A B S T R A C T

Nanohybrid hydrogels based on pristine graphene with enhanced toughness and dual responsive drug delivery feature is opening a new era for smart materials. Here pristine graphene hydrogels are synthesized by *in situ* free radical polymerization where graphene platelets are the nanobuiliding blocks to withstand external stress and shows reversible ductility. Such uniqueness is a mere reflection of rubber-like elasticity on the hydrogels. These nanobuilding blocks serve also the extensive physisorption which enhances the physical crosslinking inside the gel matrix. Besides the pH-responsive drug release features, these hydrogels are also implemented as a pulsatile drug delivery device. The electric responsive drug release behaviours are noticed and hypothesized by the formation of conducting network in the polyelectrolytic hydrogel matrix. The hydrogels are also tested as good biocompatibility and feasible cell-attachment during live-dead cell adhesion study. The drug release characteristics can also be tuned by adjusting the conducting filler loading into the gel matrix. As of our knowledge, this type of hydrogels with rubber-like consistency, high mechanical property, tunable and dual responsive drug delivery feature and very good human cell compatible is the first to report.

1. Introduction

Hydrogels are three dimensional network structured soft materials with significant amount of water retention character. Hydrogels can be developed by either chemical crosslinking or physical crosslinking (van der Waals interaction, ionic interaction, microcrystalline formation or H-bonding). Hydrogels have extensive applications encompassing biosensors [1], actuator [2], tissue scaffolds [3], smart devices [4], biocompatible alternates [5], sustained drug release [6–8] and controlled stimuli responsive drug delivery systems [9,10]. But the major demerits of hydrogels like their mechanical robustness and lack of conductivity restrict their uses in wide domain of applications [11]. Tough and highly ductile hydrogels already been reported by several researchers in previous reports which were fabricated by the concept of star shaped macromonomers and double networks [12–14].

Electrically conducting hydrogels with stimuli responsive character and mechanical superiority are basically a premium class of hydrogels which can be developed by either insertion of conducting particulates in the hydrogel matrix [15] or preparing from conjugated polymers

[16]. The second method is limited due the poor processibility and inbuilt rigidity of the conjugated macromolecular chains. But the first one i.e. adding of conducting particles seems to be more promising. Almost all the carbonaceous particles are much trustworthy in this context for achieving conductivity. CNTs already have been nurtured in research field since long days ago to toughen or reinforce polymers [17–21] and to develop composite conducting hydrogels [22,23]. CNTs are also much accepted in this field but became limited due to their complex processing, non-ecofriendliness, debundling, difficulty in dissolution and obviously expensive issues.

Compared with CNTs, graphene has been introduced due to its exceptional Young modulus (1 TPa), electrical conductivity (6000 S/cm) and high surface area (2630 m^2/g). Pristine graphene is a monolayer of graphite owing sp^2 hybridized catenated carbon atoms in s honey-comb lattice array [24]. Pristine graphene has been usually manufactured by chemical vapour deposition, and epitaxial gradual growth method. But the major demerits of these methods are (a) their lack of miscibility in polar solvents due to surface inertness of the graphene sheets, (b) high lateral dimension and (c) relatively low yields. Generally, graphene

oxide with high amount of polar functionalities has many disorders like sp^2 to sp^3 of the carbon skeleton due to over oxidation which results very little or no conductivity. Vinylic monomer based graphene nanocomposite hydrogels already have been widely studied [25–28]. In this context, polyacrylamide was used widely by many researchers. But to achieve better pH sensitivity and electrical conductivity with mechanical robustness in one composite hydrogel system, polyacrylic acid was a desirable choice. Very little work have been reported on graphene filled polyacrylic acid chemically crosslinked composite hydrogels [29,30]. The cause behind this is graphene platelets are not much prone to dispersed uniformly in acidic solution rather it has been noticed that in alkaline environment graphene showed better dispersibility. Graphene oxide filled polyacrylic acid hydrogel was reported by Shen et al. by chemical crosslinking procedure [15]. But that type of hydrogel exhibited very little conductivity and low fracture strength. In another report, compressive strength was evaluated which showed better than the previous one with a better compatibility between graphene oxide sheets and polyacrylic acid [29]. To add an extra advantage of electrical conductivity, reduced graphene oxide impregnated hydrogels have been a developed which showed better mechanical strength as well low electrical percolation.

After studying various reports we inspired to achieve graphene based pH-responsive and mechanically robust nanocomposite hydrogels by varying the synthesis parameters. We here developed polyacrylic acid based chemically crosslinked high strength composite hydrogels after arresting of graphene nanosheets by *in situ* free radical polymerization technique. Our as prepared composite hydrogels were not only show good strength but also exhibited low percolation threshold of electrical conductivity at 1.2 wt%. The composite hydrogels are found pH-responsive which is very much acceptable to fabricate smart devices. We also performed small angle neutron scattering (SANS) experiments which gave the idea of fractal formation in the hydrogel matrix. The connecting pathway in the matrix is the key concept to be an electrically conductive smart device which was also been supported by the SANS study. The quite impressive belongings of the as developed composite hydrogels are explained from the viewpoint of the hydrogel fabrication and its structural characteristics.

2. Experimental

2.1. Materials

Expanded graphite (EG) was offered by Asbury Carbons (CAS# 7782–42-5, grade 3805). The non-ionic water soluble solution phase stabilizer, Poly(acrylic acid) (PAA) with molecular weight of 3.6×10^6 g mol^{-1}, monomer acrylic acid (AA), divinylic crosslinker N,N-methylenebisacrylamide (MBA) and ammonium persulfate (APS) were purchased from Sigma Aldrich. All were used as received.

2.2. Stable pristine graphene aqueous dispersion

PAA solution (0.5% v/V) was added to deionized (DI) water in 32 °C and agitated in a magnetic stirrer for 3 h to obtain a clear solution. EG (40 mg/mL) was then added into the PAA solution and probe sonicated at 12 W power for 2 h. The dispersion was then centrifuged (Remi laboratory) at 6000 rpm to remove larger aggregates. The supernatant was collected for characterizations and preparation of the graphene-polyacrylic acid composite hydrogels.

2.3. Freeze drying of water-dispersible graphene

PAA stabilized graphene dispersions in aqueous medium were freeze dried using a Vitris Benchtop Freeze Dryer over a period of at least 24 h. After completion of freeze drying period, a greyish powder was obtained. This freeze-dried PAA-stabilized graphene was re-dispersed prior to *in situ* gelation without ant tip sonication.

2.4. Vacuum filtration for estimating graphene in aqueous dispersion

A regular vacuum filtration unit was set up to measure the concentration of solid graphene content in the PAA-stabilized graphene dispersion. A polytetrefluoro ethylene membrane with an average pore size of 0.02 μm was utilized. The formula use for this measurement is given below:

[graphene] = (final membrane mass-initial membrane mass)
/volume of the solvent

2.5. Preparation of graphene-Poly(acrylic acid) (G-PAA) hydrogels

A series of nanocomposite hydrogels were synthesized by chemical crosslinking method. Initially pure polyacrylic acid hydrogels were prepared using AA, MBA and APS. AA monomer was primarily dissolved in DI water (20% total monomer concentration). MBA (1 wt% with respect to monomer) and APS (0.5 wt% with respect to monomer) were then added into the monomer mixture and stirred with application of heat (55°–60 °C). Similarly, for synthesizing nanocomposite hydrogels the same total monomer concentration was maintained. In this case the monomer, MBA, APS and reduced graphene were added into specified amount of DI water. After that the procedure was obeyed as before.

2.6. Characterizations

2.6.1. Transmission electron microscopy (TEM)
Suspended graphene sheets were the visualization of bare HNT surface and Polydopamine capping onto the surface of HNT were done by a JEM-2100 transmission electron microscope (JEOL, Japan) at accelerating voltage of 120 kV. Composite gel was cut at subzero temperature (-70 °C) by Leica cryomicrotome cutting machine.

2.6.2. Field emission scanning electron microscopy (FESEM)
The pure and graphene containing hydrogel samples were flash frozen with sudden quenching by liquid nitrogen followed by freeze drying (Vitris Benchtop Freeze-Dryer) for overnight to prepare dry aerogel type sampels. The surface morphology of the fractured hydrogels were observed in a FESEM (field emission scanning electron microscope, MERLIN with tungsten filament; Carl ZEISS, SMT, Germany) with the accelerating voltage set to 15 kV. Before surface scanning all samples were sputter coated at 10 kV and 10 mA current for 2 min at a rate of 10 nm min^{-1}.

2.6.3. UV–Vis spectrophotometry
UV–visible spectrum of graphene dispersion in PAA was performed in Perkin Elmer UV–vis spectrophotometer lambda 35 at a wavelength range of 200–800 nm. To eliminate the effect of polymer (here PAA), the reference was fixed as PAA solution without graphene.

2.6.4. X-ray diffraction (XRD)
The materials crystal structure was characterized by powder Xray diffraction. X-ray diffraction (XRD) was used to investigate the layered structure of raw graphite and graphene sheets. The X-ray diffractometer (model: X'Pert PRO, made by PANalytical B.V., The Netherlands) was tuned to Cu-K$_\alpha$ radiation at 35 kV and 12 kW (λ = 0.15406 nm). Spectra were collected under a reflection mode at 1 min^{-1} between $2\theta = 0$–40°.

2.6.5. Raman spectra
Surface Enhanced Resonance Raman (SERR) data was accumulated by using a Trivista 555 spectrograph (Princeton Instruments) and utilizing 647 nm excitation from Kr$^+$ laser (Coherent, Sabre Innova SBRC-DBWK). An acquisition time of 120 s was applied for each spectrum in