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Enhancement of mechanical properties of nanohydrogels based on natural gum with functionalized multiwall carbon nanotube: Study of swelling and drug release

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ABSTRACT

In this study, a series of nanohydrogels based on tragacanth gum (TG) were synthesized in the presence of different amounts of glycerol diglycidyl ether (GDE) and functionalized multi-walled carbon nanotube (CNT). The gel content of prepared nanohydrogels (TG-GDE-CNT) showed dependence on the weight ratios of TG:GDE:CNT. The obtained nanohydrogels were characterized by using different techniques such as scanning electron microscope (SEM), tensile strength test, dynamic mechanical thermal analysis (DMTA) and thermal gravimetric analysis (TGA). The swelling behavior of prepared nanohydrogels showed significant dependence on the gel content, pH, and contact time. The hydrogels samples contained CNT showed superior mechanical and swelling properties than samples without CNT, (TG-GDE). The TG-GDE sample contained 0.4% w/w CNT showed an increase of 51% and 250% in tensile strength and tensile modulus, respectively, compared to sample without CNT. The loading and *in-vitro* release of Indomethacine (IND) as a model drug was investigated at pH 2, 7.4 and 9. The total loading and release showed dependence on the network structure of hydrogels and was in the range of 65–94% and 88–98%, respectively.

1. Introduction

Hydrogels are three-dimensional hydrated network formed by crosslinking polymers through either covalent bonds or non-covalent interactions [1]. Hydrogels have been extremely useful in biomedical and pharmaceutical applications such as drug delivery and tissue engineering mainly due to their high water content and rubbery nature which is similar to natural tissue, as well as their biocompatibility [2]. Hydrogels can be prepared from polymers derived from nature, synthesis and combination of nature/synthesis [3–6]. Hydrogels based on naturally derived polymers usually possess innate biocompatibility and biodegradability. Although biomaterials already contribute greatly to the improvement of health, the need exists for better polymer, fine structural modifications of natural polymers and improved methods of characterizing them [7,8]. Gum tragacanth is a hydrophilic, viscous, odorless, tasteless, non-toxic and medicinally important polysaccharide obtained from sap which is drained from the root of the plant. It consists mainly of two fractions; water-soluble (tragacanthin, 50–75%) and water-swellable (bassorin, 25–50%) [9–12]. Molecular weight of a typical gum has been reported to be about 840 kDa, calculated by Svedberg's method [13]. It has been demonstrated that different Gum tragacanth samples obtained from different species of Astragalus have different composition, and produce different levels of soluble and insoluble gum fractions [10,14]. Galacturonic acid is high in the soluble part of all species whereas L-fucose and partially xylose was major in insoluble fraction [14]. It was suggested that tragacanthin is based on essentially linear chains of 1,4-linked α-D-galacturonic acid residues [15]. The other sugars produced on hydrolysis are β-D-galactose, α-L-fucose (6-deoxy-L-galactose), β-D-xylose, and L-arabinose. The majority of these residues carry xylose-containing side-chains through C-3. A study of the structure of Bassorin (arabinogalactan) established that the polymer is composed of interior chains of D-galactopyranose residues, in which the majority of units are joined by 1,6-linkages and to lesser degree by 1,3-linkages [12,16]. Gum tragacanth solutions are acidic, usually in the pH rang of 5–6, and is fairly stable over a wide pH rang [16,17]. Gum tragacanth has been used for many years as a stabiliser, thickener, emulsifier and

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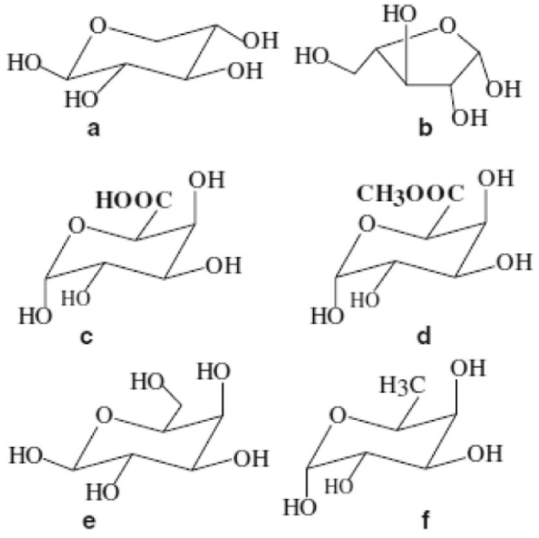
suspending agent in the food, pharmaceutical, cosmetic, textile and leather industries [18]. The main structural units of Gum tragacanth are shown in Scheme 1.

Carbon nanotubes (CNTs) with cylindrical nanostructure and walls formed by one-atom-thick sheets of carbon [19], have extraordinary thermal conductivity, mechanical and electrical properties which are valuable for nanotechnology, electronic, optics and other fields of material science and technology [20–23]. CNT also find applications as additives to various structural materials [24–28]. CNTs are categorized as single-walled-nanotube (SWNTs) and multi-walled-nanotubes (MWNTs) [29]. The chemical bonding of CNT is composed entirely of sp^2 bonds, similar to those of graphite [30], which are stronger than the sp^3 bonds and provide nanotubes with their unique strength [31]. CNT can be oxidized using strong acids, resulting in the reduction of their length while generating carboxylic groups, which increase their dispersibility in aqueous solutions [27].

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect [32,33]. Now, the drug delivery vehicle is transformed into biocompatible or biodegradable non-toxic natural or synthetic polymers that are eliminated harmlessly from the body. Due to physio-chemistry similarity (both compositionally and mechanically) between hydrogels and native extracellular matrix, hydrogels can also serve as dual-propose devices, acting as a supporting material for cells during tissue regeneration as well as delivering a drug payload.

In this study, a series of nano hydrogels based on tragacanth gum (TG) carbohydrate (Katira) was synthesized in the presence of different amounts of glycerol diglycidyl ether (GDE) and functionalized multi-walled carbon nanotube (CNT). The obtained nano hydrogels were characterized using different techniques such as scanning electron microscope (SEM), tensile strength test (Tensile), dynamic mechanical thermal analysis (DMTA), and thermal gravimetric analysis (TGA). The swelling behavior of the prepared nano hydrogels was studied under variation of pH, immersion time and temperature. The loading and *in-vitro* release of Indomethacin as a model drug was investigated at different pH values.



Scheme 1. The main chemical building blocks of the carbohydrate biopolymer tragacanth gum. a) β-D-xylose, b) L-arabinose, c) α-D-galacturonic acid, d) α-D-galacturonic acid methylester, e) β-D-galactose, f)α-L-fucose.

2. Experimental section

2.1. Materials

Tragacanth Gum (TG), Katira, was purchased from local pharmaceutical shop and washed thoroughly with distilled water several times. Glycerol diglycidyl ether (GDE) was purchased from Sigma Aldrich (Germany). Carboxylic acid functionalized multiwall carbon nanotube (CNT), NaCl, NaOH, HCl(37%), acetone, and N, N-dimethyl formaldehyde (DMF) were purchased from Merck Chemical Co and Na_2HPO_4 and K_2HPO_4 from Fluka (Darmstadt, Germany). All the chemicals and reagents were analytical grade and used as received without further purification. pH adjustments were performed with HCl (1 M) and NaOH (1 M) solutions.

2.2. Synthesis

2.2.1. Synthesis of TG-GDE hydrogel

In a round-bottom flask equipped with a magnetic stirrer, 1.0 g TG was poured in 100 mL distilled water and stirred at 60 °C for 3 h to obtain a homogeneous solution, and then pH of the solution was adjusted at 11 by NaOH (1 M) and stirred at 60 °C for 15 min. Then in an alkaline environment, a solution of GDE (1.5 g) in DMF (20 mL) was added and the reaction was completed by stirring and heating at 60 °C under nitrogen atmosphere for 24 h. Finally, the reaction was poured in excess of acetone to complete precipitation. The precipitate was filtered and dried in a vacuum oven overnight at 40 °C.

2.2.2. Synthesis of TG-GDE-CNT hydrogels

In a round-bottom flask equipped with a magnetic stir bar, a homogeneous solution of TG in distilled water was prepared and adjusted at pH 11. Then a certain amount of CNT (as shown in Table 1) was dispersed in water (15 mL) with ultrasonic mixer and added to the homogeneous TG solution, the mixture was stirred for another 30 min. Afterward, solution of a certain amount of GDE in DMF (Table 1) was added to the above prepared mixture. The reaction mixture was purged with nitrogen and stirred at 60 °C for 24 h to complete. Finally, the reaction mixture was poured in acetone. The formed precipitate was filtered, washed with water and dried under vacuum overnight at 40 °C.

2.3. Determination of molar concentration of COOH groups in TG and CNT

To define the molar concentration of COOH groups in both TG polymer and CNT, titration and back titration analyses were used, respectively. The mmol of COOH groups in 1 g of TG was measured by titration. 1 g TG was dissolved in 100 mL distilled water and then COOH groups of TG were neutralized by addition NaOH solution (1 M) to the equivalence point of titration. For CNT which is not soluble in water, back titration was used to determine the COOH groups. 2 mg CNT was dispersed in 60 mL NaOH solution (2 g NaOH in 60 mL deionized water, 0.8 M) at room temperature and stirred

Table 1
Formulations for preparation of Nano hydrogels.

Nanohydrogels	TG (g)	GDE (g)	CNT (g)
TG-GDE	1	1.5	–
TG-GDE-CNT1	1	1	0.01
TG-GDE-CNT2	1	1.5	0.01
TG-GDE-CNT3	1	2	0.01
TG-GDE-CNT4	1	3	0.01
TG-GDE-CNT5	1	1.5	0.001