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Investigation on pH/salt-responsive multifunctional itaconic acid based polymeric biocompatible, antimicrobial and biodegradable hydrogels

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ABSTRACT

The present investigation focused on a new kind of pH-tunable IAD polymeric hydrogels based on itaconic acid (IA), acrylic acid (AA) and diethylene glycol (DEG), were synthesized by free radical polymerization viz. organic solventless approach and they were characterized by FT-IR, SEM analysis. For successive biocompatible hydrogels, biological activities were mainly considered for investigation. The swelling studies showed that the IAD hydrogels exhibited significantly greater pH-responsive swelling in alkaline medium and achieved up to 2200%. The salt responsive behaviour of IAD hydrogels proved that the results of swelling equilibrium decreased with increasing charge of the cation. Since, the prepared hydrogels were anionic in nature, excellent antibacterial zone of inhibition achieved towards gram + ve pathogens. It was found that the IAD hydrogels were performed better antifungal zone of inhibition against *C. albicans*. The IAD hydrogels pronounced noticeable zone of inhibition towards various pathogens even for pristine (without antibiotic) samples. The prepared itaconic acid based hydrogels were nontoxic due to their IC-50% values. The IAD hydrogels underwent for biodegradation due to n-number of ester moieties. It facilitated, hydrolysis of polymeric skeleton and achieved 88% of degradation. It was found that IA based pH-sensitive polymeric hydrogels were nontoxic with aggregable biomedical properties.

1. Introduction

Hydrogels are the first biomaterial recognized by human being for biomedical applications [1]. Hydrogels are distinctly maintained three dimensional crosslinked polymeric networks. Hydrogels can imbibe huge amount of water or deswell with respect to external environmental conditions such as temperature, pH medium, magnetic field, electric field and ionic strength etc. [2–4]. Hydrogels are widely used in biomedical applications due to their exclusive swelling properties, easy method of formulation, biocompatibility, and desirable physical and chemical properties [5]. Polymeric hydrogels are significant material having potential application in the biomedical field, such as tissue engineering, soft contact lenses, protein delivery, gene delivery, drug delivery and burn dressing [6]. Hydrogels have also found peculiar interest in pharmaceutical applications. Hence, they play a key role in drug formulation, drug administration, sustainable drug release behaviour, site specific drug delivery and drug carriers etc. [7–12]. The stimuli sensitive polymers have excellent release efficacy of therapeutic agents [13]. The pH-sensitive hydrogels have been utilized broadly in the biomedical field. In general, the swelling nature of pH-sensitive hydrogels was affected by varying environmental pH. Therefore, they were hopeful mechanism for site specific drug delivery system [14]. Hydrogel possess itaconic acid and acrylic acids in their polymeric composition are FDA approved compounds. Itaconic acid is non-toxic due to the availability from natural resources, high permeability and biodegradable in nature [15–17].

Itaconic acid based polymeric hydrogels have get attracted towards biomedical field due to their vast biological properties. Intrusion of even small amount of itaconic acid in a polymeric chain promotes, complexation and pH-sensitive swelling nature of hydrogels. This trend increases with increasing the amount of itaconic acid during polymerization. Itaconic acid possesses two carboxylic moieties in its skeleton. Therefore, when it interacts with the suitable swelling medium and pH, responds to electrostatic repulsion leading to improved

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swelling behaviour [18]. In general, the comparison between itaconic acid and acrylic acid in the same polymerization reaction, itaconic acid shows more pendent carboxylic group than the acrylic acid. Hence, the availability of itaconic acid in the polymeric back bone increases the number of carboxylic acid moieties. On the other hand, availability of carboxylic groups in polymeric chain, accept the proton at lower pH and donate the proton in higher pH, provided the electrostatic repulsion causes swelling ability of hydrogels [19]. Acrylic acid is an anionic in nature so it is also used to prepare pH-sensitive hydrogels. Acrylic acid based hydrogel shows varying swelling behaviour in response to change in environmental pH medium. It gives low swelling nature in acidic medium and high swelling nature in basic medium [20–21]. Several researches have shown that acrylic acid exerts strong influence on swelling nature of hydrogels [22–23]. In addition, the future of polymer will be focused on the integration of new functionalized materials. At the beginning and application of functionalized polymers achieved through esterification and crosslinking process to obtained desire properties. For instance, M. U. Khan et al. [24] have prepared surface modified carbon nanotubes via in situ emulsion polymerization, K. R. Reddy et al. [25] prepared PANI and TiO_2 based nanocomposite by in-situ chemical oxidative polymerization, S. H. Choi et al. [26] have reported graphene based nanocomposite, K. R. Reddy et al. [27] synthesized iron oxide-conjugated environmentally stable composite, D. R. Son et al. [28] polyester based TRG composites, M. Hassan et al. [29] synthesized graphene oriented nanocomposite via emulsion polymerization, H. Mackova et al. [30] reported degradable HEMA based hydrogels, K. R. Reddy et al. [31] prepared organosilane based nanocomposite, K. R. Reddy et al. [25] synthesized TiO_2 based photolytic degradable nanocomposites, Y. P. Zhang et al., [33] reported UV treated SiO_2/Poly(3-aminophenylboronic acid) based nanocomposite [24–33]. Since, the present investigation was also prepared itaconic acid based hydrogels through functional group modified methodology.

The antimicrobial inhibition is one among the valuable property in the field of biomedical applications. Hence, the anticipation of appearance of microorganism is very important in biomedical application. Consequently, in recent years, infections are the most common cause of biomaterial implant failure such as wound dressings, contact lenses, and artificial skin and in drug release systems and pharmaceutical applications [34–35]. In general, infections generally caused by different bacteria and fungi. For instance, the majority of tissue implant infections are caused by *S. aureus*[36]. As a result, antibacterial activity is one of the most valuable properties in the biomedical applications. Moreover, infections by bacterial and fungal adherence on the biomaterial are the initial step. It is followed by colonization and renders the antibiotic treatment which made the defense mechanism as ineffective. In contrary, the present investigation focused towards antimicrobial hydrogel without any metal ion and other metal complexes [37]. The itaconic acid based hydrogel have produced antimicrobial zone of inhibition against various anti-microbial pathogens even for pristine (without antibiotic) samples. It has been brought up that hydrogels encompassing carboxylic moieties (such as itaconic acid and acrylic acid) are highly anticipated in biomaterials.

Previously, D. Saraydin et al. have prepared crosslinked Acrylamide-maleic acid hydrogels and radiation induced acrylamide/crotonic acid hydrogels [38–39]. J. Rosiak et al. have also prepared acrylamide based for agricultural processing [40]. However, the improper use of these contaminants by farmers causes eutrophication leading to problem in nitrogen cycle. Moreover, nitrate pollution causing blue baby syndrome. Many researchers devoted their studies for environmental pollution control [41]. Since, the prepared hydrogels from natural resources (itaconic acid and acrylic acid), may be an important application to help prevent environmental pollution more in future

In this paper, the attention has been focused a simple approach for the preparation of itaconic acid and acrylic acid based pH-sensitive hydrogels using $K_2S_2O_8$ as initiator and N, N′-Methylene bis-acrylamide as cross linker at 65 °C (optimized temperature) with organic solventless approach. The diethylene glycol additional *co*-monomer used to increase the chain length of pre-polyester. It facilitated the ester moieties in the polymeric backbone. In general, ester groups are easily hydrolysable in contrary to other functional groups. Hence, it facilitated the biodegradation process quickly. The synthesized itaconic acid based hydrogels were characterized for morphology, pH- sensitive swelling, inorganic salt removal, crystalline, thermal, biological properties, and cell viability and degradation properties. From the present investigation, the resultant polymeric biocompatible hydrogels may be recommended as good biomaterial as well as for pH-sensitive drug delivery system more in future.

2. Experimental

2.1. Materials

Itaconic acid (IA) was supplied by the Sigma Aldrich Company (Bangalore, India) diethylene glycol (DEG) and acrylic acid (AA) were purchased from Merck (Germany). AA was vacuum distilled at 54 °C/25 mmHg to remove the inhibitor hydroquinone. Potassium per sulphate ($K_2S_2O_8$) was purchased from Merck. N, N′-Methylene bis-acrylamide from Sigma Aldrich (USA). Double distilled water was used for preparation of the buffer solution. Double distilled water was used for experiments.

2.2. Preparation of itaconic acid based swellable hydrogel

The pH-sensitive polymeric hydrogels of various compositions were performed by free radical polymerization, according to the modified procedure, reported previously [42]. First, the equimolar mixture of itaconic acid (0.01 mol) was dissolved in double distilled water and diethylene glycol (0.04 mol) was added to the aqueous monomeric solution in the polymerization flask at 65 °C for 30 min with constant stirring in an inert nitrogen atmosphere to prepare pre-polyester. Then, the initiator $K_2S_2O_8$ (0.05 g) and cross linker N, N′-Methylene bis-acrylamide (0.05 g) were also directly added in the flask with a stoichiometric amount of acrylic acid (0.025 mol). The free radical polymerization was continued for 1 h and 30 min at 65 °C (optimized temperature) with perpetual stirring in a nitrogen atmosphere. The formation of pale yellowish insoluble gel deliberated the completion of the polymerization reaction. The sequence of itaconic acid based hydrogels have been prepared using a constant ratio of AA while altering the stoichiometry of selected monomers of itaconic acid and diethylene glycol (Scheme.1). The prepared hydrogels were submerged in double distilled water at room temperature for about seven days. During this period, water was replaced twice in a day with fresh water in order to eradicate residual monomers. Afterwards, hydrogels were dried at room temperature to obtained constant mass. The representation and description of itaconic acid based hydrogels have shown in (Table.1). The best system has been considered for further evaluation.

2.3. FT-IR studies

FT-IR spectroscopy was performed at room temperature using an Alpha Bruker Fourier-transform infrared spectrometer (FTIR), with a resolution of 2 cm^{-1}. The spectrum over the wavelength range was 4000 and 400 cm^{-1}

2.4. MALDI-TOF mass spectroscopy analysis

The matrix assisted laser desorption ionization (MALDI) Bruker time of flight instrument (Autoflex III Smart beam) equipped with an Nd-YAG (neodymium-doped yttrium aluminum garnet) 355 nm solid state laser. An accelerating voltage of 20 kV was used. The mass spectra were recorded in the reflector mode. The $I_1A_1D_4$ hydrogel was dissolved in