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Synthesis and in vitro behavior of iron-crosslinked *N*-methyl and *N*-benzyl hydroxamated derivatives of alginic acid as controlled release carriers

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Abstract

N-methyl and *N*-benzyl hydroxylamines were synthetically conjugated to alginic acid to produce hydroxamated derivatives with different degrees of substitution. The new polymeric materials were used to form coordinate complexes with iron(III). The hydroxamated derivatives as well as their iron complexes were characterized using infrared spectroscopy and differential scanning calorimetry.

Phenobarbitone-loaded and blank beads were prepared utilizing the new iron-crosslinked hydroxamated polymers and evaluated with respect to their ability to control drug release, as well as their iron leaching properties.

The iron-crosslinked polymeric composites proved capable of encapsulating the model drug and sustaining its release in the dissolution media, the release profiles were sensitive to the type and degree of substitution.

Keywords: Benzyl hydroxamated alginic acid; Methyl hydroxamated alginic acid; Ionic cross-linking; Iron complex; Beads; Controlled release; Phenobarbitone

1. Introduction

Metal–polymer composites are coordination-type complexes that are formed by coordinate bonds in which a pair of electrons is transferred from an electron donor to an electron acceptor. Coordination complexes consist of a central metal ion bonded to an electron-pair donor (a ligand); the complex may be neutral or charged [1].

Polymer–metal composite materials have been utilized in drug delivery, mainly in the development of sustained release oral drug delivery systems. Crosslinked alginate, chitosan and carboxymethylcellulose have been reported as examples of such systems [2–13].

Of the above mentioned polymers, alginate seems to be the most commonly used in the preparation of polymer–metal composites [4–14]. Alginates are

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linear unbranched polysaccharides containing two uronic acids: β-D-mannuronic acid and α-L-guluronic acid, the gelation of alginates occurs by cross-linking of the uronic acids with cations, mainly calcium ion.

However, calcium–alginate complexes were reported to show major shortcomings related to the pronounced sensitivity of the release profile towards the composition of the release medium [7–11].

In one report, the cross-linking calcium ions appeared to be rapidly discharged from calcium alginate matrices in acidic media to yield the protonated alginic acid. This transformation reduced the degree of cross-linking within the matrix, thus destroying its ability to provide controlled drug release [8].

On the other hand, in NaCl solutions and simulated intestinal fluid, calcium ions were partly exchanged by the non-gelling sodium ions or sequestered by phosphate. This caused swelling and dissolution of the matrices, thus inducing rapid release of the encapsulated drug [7,9].

This prompted us to search for more stable alginate-divalent ions complexes. Our focus was directed towards iron-hydroxamate complexes because of their extraordinary stability under various pH conditions [15,16]. Such complexes have been utilized for analytical [1], and clinical purposes [17].

We have used ferric ions to crosslink hydroxamated alginic acid, thiolated alginic acid and hydroxamated chitosan succinate, resulting in polymeric matrices that exhibited relative pH independent and sustained drug release profiles [18–20]. However, only non-substituted hydroxamic acid moieties were used.

The aim of this study was to synthesize *N*-methyl, and *N*-benzyl hydroxamated polymers, and to establish the effect of these substituents on the release properties, additionally, it was anticipated that the lipophillic methyl and benzyl groups will improve the drug loading capacity of the semisynthetic polymeric derivatives.

2. Materials and methods

2.1. Materials

The following chemicals were purchased from the corresponding companies. All chemicals were used as obtained from the manufacturers without further purification. Sodium alginate (Hayashi Pure Chemical Industries Ltd., Osaka, Japan), dicyclohexylcarbodiimide DCCI (Fluka, Switzerland), hydroxylamine hydrochloride (ACROS, USA), *N*-methyl hydroxylamine hydrochloride (Fluka, Switzerland), *N*-benzyl hydroxylamine hydrochloride (Fluka, Switzerland), ferric chloride anhydrous LR (S.D. Fine-Chem. Ltd., Boisar, India), potassium dihydrogen phosphate (S.D. Fine-Chem. Ltd., Boisar, India), potassium thiocyanate (Scharlau, European Union), magnesium sulphate dried (Vickers Laboratories Ltd., Burley, UK), phenobarbitone (May & Baker Ltd., Dagenham, UK), sodium hydroxide (Lanover House, UK). All solvents (chloroform, acetone, ethanol, diethyl ether, pyridine, and hydrochloric acid) were of analytical grade (Gainland Chemical Company, UK).

2.2. Polymer synthesis and bead preparation

2.2.1. Synthesis of N-methyl- or N-benzyl-hydroxamated alginic acid derivatives (MHAA and BHAA)

The reaction was carried out according to our previously reported method [18,19]. Sodium alginate (5 g, equivalent to 0.0225 mol carboxylate) was dissolved in water (250 ml), then hydrochloric acid solution (1.0 N) was added dropwise to the stirred polymer solution till a pH of 4.0–4.5 was attained. Subsequently, DCCI (1.86, 2.79 and 4.64 g, equivalent to 0.009, 0.0135 and 0.0225 mol) was added to the stirred mixtures to activate 40%, 60% and 100% of the carboxylic acid groups. After 2 h, *N*-methyl hydroxylamine hydrochloride (3.01, 4.51 and 7.52 g, equivalent to 0.036, 0.054 and 0.090 mol, respectively) or *N*-benzyl hydroxylamine hydrochloride (2.87, 4.31 and 7.18 g, equivalent to 0.018, 0.024 and 0.045 mol, respectively) was added to the mixture and the reaction was further stirred for 1 h.

Afterwards, the pH of the reaction was raised to 6.0 using sodium hydroxide solution (1.0 N), and the reaction was stirred for 2 h. Thereafter, the pH was raised again to 9.0, and the reaction mixture was stirred over 24 h at room temperature. The white precipitation of dicyclohexylurea was removed by filtration and then the polymeric material was precipitated with concentrated HCl (10 ml) and acetone (250 ml) then filtered and washed thoroughly with ethanol (3×100 ml), followed by acetone (3×100 ml) and diethyl ether (200 ml), respectively. The resulting mass was left to dry at room temperature overnight. After drying it was milled by mortar and pestle.