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Synthesis and in vitro evaluation of alginate-cellulose nanocrystal hybrid nanoparticles for the controlled oral delivery of rifampicin

Deepa Thomas[a,c], M.S. Latha[b,c,*], K. Kurien Thomas[a]

[a] Research and Post Graduate Department of Chemistry, Bishop Moore College, Mavelikara, Kerala, India
[b] Department of Chemistry, Sree Narayana College, Chengannur, Kerala, India
[c] Department of Chemistry, Sree Narayana College, Kollam, Kerala, India

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ABSTRACT

Polymeric nanoparticles have the potential to overcome the barriers associated with oral drug delivery to protect the drug from the harsh gastric conditions and provide controlled release of the drug in the target area. Nanoparticles have the advantage of size-dependent intestinal uptake. In this study, the size of rifampicin-loaded alginate cellulose nanocrystal hybrid nanoparticles was considerably reduced to 100 nm using probe sonication. The synthesized nanoparticles exhibited pH-dependent swelling and an in vitro drug release profile. Preliminary studies on the biocompatibility of the nano particles using an MTT assay established the non-toxic nature of the particles. The net result of the introduction of the cellulose nanocrystals into the alginate highlighted the higher encapsulation efficiency and the sustained release profile of the drug. In conclusion, rifampicin-loaded polymer nanoparticles have a better outcome for the treatment of *Mycobacterium tuberculosis*.

1. Introduction

Oral delivery is the preferred route of drug administration because it is simple, comfortable, economic, secure, and non-invasive [37]. Polymeric nanoparticles have attracted considerable attention, as they may be able to overcome many of the challenges associated with oral delivery [11]. Particle size plays a crucial role in intestinal uptake and in vivo distribution [25,39]. Particles below 100 nm have been shown to provide a 15- to 250-fold higher cellular uptake than micro particles in studies conducted on a rat model [46]. Particles with a size less than 5 nm were rapidly cleared from blood via extravasation or renal clearance. However, polymeric nanoparticles in the 20–100 nm range avoid renal clearance and remain in the blood for a long period of time [13]. The nano sized particles have a higher surface area and high mechanical strength [43,47,67] and can extravasate through tumours, epithelium or endothelium to allow efficient delivery of a drug [64].

There are many reports on using alginate-based microparticles as a drug carrier [15,27,40,49]. Alginate (ALG) is a naturally occurring, anionic copolymer of guluronic (G) and mannuronic (M) acids and is widely used in the bio encapsulation of drugs, proteins and cells. It is biodegradable, biocompatible, non-toxic, and mucoadhesive; exhibits pH-dependent swelling properties; and has the ability to form a gel in the presence of divalent cations such as calcium [59]. However, limited mechanical stability, durability, and high-diffusion rates resulting from high porosity restricted the application of alginate in the field of drug delivery [35]. To improve its properties, a variety of synthetic and natural polymers have been proposed for blending with alginate [6,15,20,21,27,41,52,55,63,68]. Most of the studies failed to achieve the desired structural stability and biocompatibility [38] or to exclude the usage of organic cross-linking agents or solvents [1,5,41,51]. Cellulose nanocrystals (CNCs), derived from cellulose, which is abundantly available, biocompatible and cheap, may be able to enhance the properties of ALG [8,34,58,65]. Cellulose possesses excellent compaction properties [24], and its blend with pharmaceutical excipients acts as an ideal carrier for oral administration.

Ooi et al. reported that the addition of CNCs to gelatine hydrogel causes a reduction in voids in the gelatine network, resulting in a more rigid hydrogel structure and preventing drug leakage [44]. The chemical structures of cellulose and ALG are similar, and both belong to the same polysaccharide family. Lin et al. observed enhanced mechanical strength and improved drug release behaviour upon incorporating CNCs into alginate micro beads. They also reported that the alginate component stabilized CNCs from aggregation [35]. In this present study, alginate-cellulose nanocrystal hybrid nanoparticles (ALG-CNC NPs) were synthesized by a green method, and the possibility of using these nanoparticles for the oral delivery of rifampicin (RIF) was evaluated.

RIF is a powerful antibiotic that is conventionally used against

* Corresponding author. Department of Chemistry, Sree Narayana College, Chengannur, Kerala, India. Tel.: +91 9400648068.
E-mail address: lathams2014@gmail.com (M.S. Latha).

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Mycobacterium tuberculosis and is the semi-synthetic hydrazine derivative of rifampicin B. The potential ability of RIF to interact with bacterial DNA-dependent RNA polymerase and the specific inhibition of bacterial RNA polymerase make it a powerful antibiotic [16]. The poor water solubility of RIF necessitates the administration of high doses of the drug to maintain the concentration within a therapeutic range for as long as treatment requires. This usually results in adverse side effects. To remedy these difficulties, different strategies have been developed. One of the major approaches is the encapsulation of RIF in a polymer carrier to provide sustained release and maintain steady plasma drug levels for extended periods of time with reduced side effects [53]. Ionic gelation is commonly used for drug encapsulation, as it is easy and does not need any emulsification steps or organic solvents. In this method, the drug to be encapsulated is mixed with the polymer solution prior to particle formation and gelation. This solution is gradually added to the cross linker with stirring. From the resultant nanospheres, the drug is physically dispersed. Originally, ionic gelation was utilized for the preparation of microparticles. Rajaonarivony et al. modified this method by complexation with poly-L-lysine for the preparation of alginate nanoparticles in a size range of 250–850 nm [51]. However, poly-L-lysine is toxic in nature and is not suitable for in vivo applications.

In the present report, pH-sensitive ALG-CNC NPs were synthesized by ionic gelation with divalent calcium ions using natural honey as a stabilizing agent. The potential of the synthesized nano particles for the sustained release of the hydrophobic drug RIF was demonstrated by in vitro studies.

2. Materials and methods

2.1. Materials

Medium viscosity sodium alginate powder (viscosity of 2% solution, 25 °C ≈ 3500 cps,Sigma-Aldrich,London), Rifampicin (Himedia laboratories, Nasik). Calcium chloride dihydrate, sodium hydroxide, hydrogen peroxide and oxalic acid (Merck, Germany) were of analytical grade and used as such without any further purification. The banana fibre was collected from local farms. Natural honey used in this study was procured from Kerala Agriculture University.

2.2. Extraction of nanocrystalline cellulose from banana fibre

Cellulose was extracted from banana fibres by steam explosion by following a reported procedure with slight modifications [9]. Chopped banana fibres (30 g) were steam exploded using a 2% NaOH (fibre to liquor ratio 1:10) solution in an autoclave at a pressure of 15 lb for a period of 2 h. The crude mass was washed with distilled water, followed by hydrogen peroxide (10%) bleaching, treatment with oxalic acid and ultrasonication for 10 min to completely extract the CNCs.

2.3. Synthesis of ALG-CNC NPs

ALG-CNC NPs were synthesized by the ionotropic gelation technique according to a previously reported procedure with slight modifications [19]. Aqueous sodium alginate solution (1%, w/v) was mixed with honey (added as a surfactant and stabilizer) at various concentrations. CNCs were dispersed into this solution followed by the addition of RIF. Aqueous calcium chloride solution (1%, w/v) was added dropwise into this solution under continuous stirring using magnetic stirrer. This homogenized mixture was sonicated for 5 min. Nanoparticles were collected by centrifugation at 3500 rpm for 5 min, washed and dried under vacuum.

2.3.1. Material characterization methods

Fourier transform infrared (FTIR) spectra of RIF, ALG-CNC NPs and RIF loaded ALG-CNC NPs were recorded between 400 and 4000 cm^{-1} using a Shimadzu FTIR model 1801. The surface morphologies of the ALG-CNC NPs were probed using a JEOL model 1200EX transmission electron microscope (TEM) operated at an accelerating voltage of 80 kV. The XRD patterns of the samples were recorded by using a Bruker D8 Advance diffractometer with monochromatic Cu-Kα_1 radiation (λ = 1.5418 Å). The particle size and zeta potential measurement was carried out using a Zetasizer Nano ZSP instrument (Malvern, UK).

2.4. Swelling behaviour

The swelling behaviour of the nanoparticles was determined by equilibrating a known mass of the nanoparticles with a solvent and allowing them to swell to equilibrium [2]. Accurately weighed dried ALG-CNC nanoparticles (100 mg) (W_d) were suspended in 10 ml solutions with different pH values (1.2, 6.8 and 7.4) for 12 h in different bottles. At predetermined time intervals, the swollen nanoparticles in the bottles were collected by centrifugation at 10,000 rpm for 10 min (SORALL® Bioguge Stratos Ultracentrifuge) and weighed immediately after carefully removing the excess liquid from the surface using filter paper (W_s). The swelling percentage was estimated using equation (1).

Data were given as the mean ± the standard deviation (SD) and based on 3 independent measurements.

$$S = \left(\frac{W_s - W_d}{W_d}\right) \times 100 \tag{1}$$

2.5. Entrapment efficiency of ALG-CNC NPs

The concentration of the free RIF was determined by measuring the absorbance at 475 nm, using a UV–VIS spectrophotometer (PerkinElmer Lambda Bio 40). The RIF content was determined by using a calibration curve constructed from a series of solutions with known drug concentrations. The entrapment efficiency percentage (% EE) was calculated as follows:

$$\%\,EE = \left(\frac{W_a - W_b}{W_a}\right) \times 100 \tag{2}$$

where W_a is the total weight of the drug fed and W_b is the weight of the non-encapsulated free drug.

2.6. In vitro drug release

In vitro drug release studies were performed in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4), as per the United States Pharmacopoeia standard. Approximately 30 mg of RIF loaded NPs was introduced into a dialysis bag with a MW cut off of 12,000 Da and incubated with 100 ml of the release medium. Release studies were conducted at 37 °C in an incubated shaker at 100 rpm [10]. At predetermined time intervals, samples (5 ml) were withdrawn, and replaced with an equal volume of freshly prepared medium and the absorbance was noted at 475 nm (for RIF) by a UV–VIS spectrophotometer (PerkinElmer Lambda Bio 40). The concentration of RIF in the medium was calculated from the standard curve. Data were given as the mean ± standard deviation (SD) based on 3 independent measurements.

The entire process for drug release in the human body is simulated by using a pH gradient assay. Initially the pH was adjusted to 1.2 to simulate the stomach for 2 h, followed by a pH of 6.8 for the next 4 h (intestine), and finally, a solution with a pH of 7.4 for 6 h (colon). At pre-determined time intervals, the drug release was measured using UV spectroscopy at 475 nm. Data were given as the mean ± standard deviation (SD) based on 3 independent measurements.

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