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Development of an injectable pseudo-bone thermo-gel for application in small bone fractures

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ABSTRACT

A pseudo-bone thermo-gel was synthesized and evaluated for its physicochemical, mechanical and rheological properties, with its application to treat small bone fractures. The pseudo-bone thermo-gel was proven to have thermo-responsive properties, behaving as a solution in temperatures below 25 °C, and forming a gelling technology when maintained at physiological conditions. Poly propylene fumerate (PPF), Pluronic F127 and PEG-PCL-PEG were strategically blended, obtaining a thermo-responsive delivery system, to mimic the mechanical properties of bone with sufficient matrix hardness and resilience. A Biopharmaceutics Classification System (BCS) class II drug, simvastatin, was loaded in the pseudo-bone thermo-gel, selected for its bone healing properties. *In vitro* release analysis was undertaken on a series of experimental formulations, with the ideal formulations obtaining its maximum controlled drug release profile up to 14 days. *Ex vivo* studies were undertaken on an induced 4 mm diameter butterfly-fractured osteoporotic human clavicle bone samples. X-ray, ultrasound as well as textural analysis, undertaken on the fractured bones before and after treatment displayed significant bone filling, matrix hardening and matrix resilience properties. These characteristics of the pseudo-bone thermo-gel thus proved significant potential for application in small bone fractures.

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1. Introduction

Approximately 2.2 million bone graft surgeries are conducted globally each year. As a result, surgeons are faced with multiple clinical challenges in bone reconstruction. Some of these challenges are defect sizes, anatomic sites, mechanical stresses and available soft tissue cover (Tanga et al., 2016). The gold standard for repairing skeletal defects is autologous bone grafting, however, this method has many disadvantages which include bone graft loss, problems relating to the surgical site, short-term instability in massive defects and autograft failure rates which is greater than 50% in complicated healing environments (Bosco et al., 2016). Due to these shortcomings, the utilization of synthetic implants is becoming increasingly popular. Nevertheless, present day biomaterials were initially fabricated for other engineering approaches, as a result, there may be many limitations such as a foreign-body reaction, infection, as well as extrusion of the implanted biomaterial (Iwase et al., 2016).

Recently, the development of injectable polymeric hydrogels and thermo-gels for the treatment of bone defects are gaining much research popularity. These systems are composed of various polymers that have specific properties that will heal the defected bone and support bone regeneration (Zhao et al., 2016; LogithKumar et al., 2016). To date, injectable thermo-gels in the field of bone tissue engineering has provided numerous advantages over former approaches. Injectable therapy has an unparalleled benefit in which complex defected areas can be effortlessly targeted without invasive methods. It can also increase the physico-mechanical properties of the damaged bone by delivering many drug molecules as well as growth factors to the site of injury (Farokhi et al., 2016).

Due to the thermo-gel possessing water based homogenous properties, it displays a remarkable platform for bone tissue engineering. It has the ability to encapsulate, manipulate and transfer its constituents to the surrounding tissue. Polymeric thermo-gels, loaded with a statin drug, has been known to increase bone repair. The polymeric gel further provides mechanical support at the site of bone injury (Nayef et al., 2016). A thermo-responsive injectable system behaves as a transitional sol-gel

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system. This occurs by reacting the injectable system to a stimulus, resulting in a change of physical and chemical properties (Ma et al., 2016). Upon gelation of the injectable thermo-gel, cellular responses and cell distribution are promoted. Due to the significant hydrated nature of the thermo-gel, simulation of the extra cellular matrix (ECM) is an essential property responsible for bone healing and repair (Jeong et al., 2016; Khoshroo et al., 2017).

To date, numerous polymers, due to their biocompatible and biodegradable properties, have been analysed for injectable delivery (Luoa et al., 2016). These polymers possess specific stimuli responsive properties, which efficiently deliver its encapsulated constituents at the site of injury (Hashimoto et al., 2015; Tang et al., 2016; Caetano et al., 2016; Caramella et al., 2016; Basha et al., 2015).

The properties of maintaining thermo-gelation refers to a system by which a substance undergoing change must in all instances be in thermodynamic equilibrium with its surroundings. The pressure and temperature of the substance should differ minimally from its surroundings at a stage of slow cycle operation. Frictional forces must be minimum, with least loss of energy due to conduction, convection or radiation during the cycle process (Santapuri, 2016; Lucia, 2016; Egner and Egner, 2016). The transition from sol to gel, correspond to a change in temperature conditions. However, once substantial energy is dissipated from the system and thermodynamic equilibrium is lost, the system will lose its gelation nature. In an injectable thermo-gel system, due to minimum interferences from its environment *in situ*, properties of its responsive nature will be preserved in a substance/material at a given temperature range. Properties such as stability, biocompatibility and biodegradability are conserved when physiological conditions are maintained (Jung et al., 2017; Nguyen et al., 2015; Denga et al., 2014).

This research focuses on the formulation of an injectable pseudo-bone thermo-gel drug delivery system, possessing considerable fluid dynamic properties as a sol-gel formulation. The formulation, loaded with a suitable active pharmaceutical ingredient (API), was evaluated for its chemical, physical and rheological properties

This paper discusses the remarkable characteristics of the pseudo-bone thermo-gel, substantially proving its potential for application in bone fracture repair, and the restoration of bone matrix hardness and resilience.

2. Materials and methods

2.1. Materials

Diethyl fumarate, 98%; diethyl ether (anhydrous); hydrochloric acid,1.85% $^{v}/_{v}$; hydroquinone, 99% purity; methylene chloride; propylene glycol (1,2-propandiol); sodium sulphate and zinc chloride were purchased from Merck (Pty) Ltd. PEG (Mw 4000), epsilon-caprolactone, 99%; stannous octoate, 92.5%; petroleum ether, 90%; pluronic F-127; poly(ethylene glycol) diacrylate and simvastatin (molecular weight: 418.57), 97% purity, were procured from Sigma-Aldrich (St. Louis, MO, USA). All other reagents were of analytical grade and were employed as received. All synthetic reactions were carried out under inert conditions.

2.2. Synthesis of poly (Propylene Fumarate) (PPF)

Poly (propylene fumarate) (PPF) was prepared by a two-step procedure involving bis(hydroxypropyl) fumarate as an intermediate owing to the relative lower by-product formation associated with this synthetic procedure, as seen in Fig. 1. Initially diethyl fumarate (30.52 g, 180 mmol) and propylene glycol (40.75 g, 540 mmol) were reacted in an oven-dried 500 mL round bottom

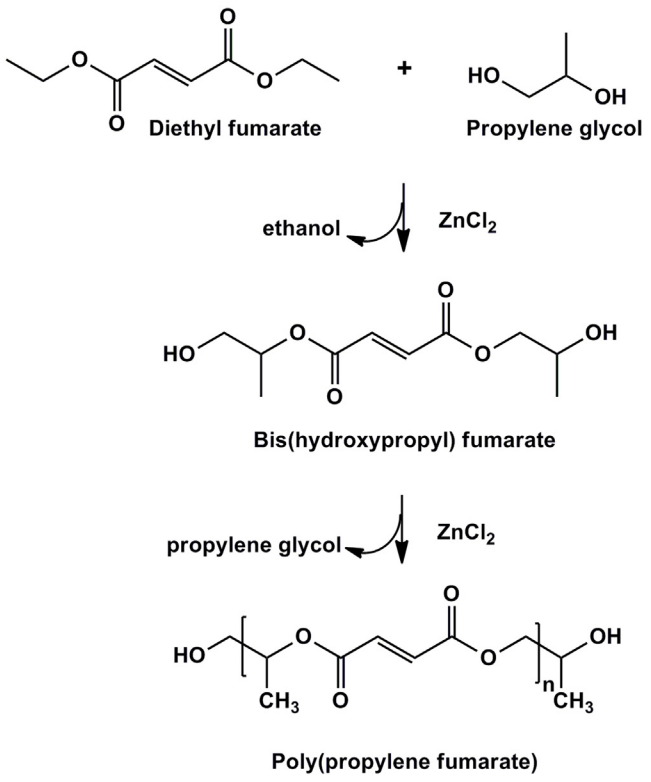

Fig. 1. Schematic representation of the synthesis for PPF, using a 2-step method involving bis(hydroxypropyl) fumarate as an intermediate.

flask (RBF), under inert conditions, at a temperature of 90 °C. To this stirred solution, the crosslinking inhibitor hydroquinone (0.0303 g, 0.266 mmol), and the Lewis acid catalyst $ZnCl_2$ (0.2 g, 1.53 mmol) was added. Thereafter, the temperature of the system was increased to 110 °C. Following this step, the temperature was gradually increased from 110 °C in increments of 10 °C every 30 min to 130 °C. This reaction step yielded the intermediate bis (hydroxypropyl) fumarate and ethanol (distillate), and the reaction was ceased when 90% of the theoretical ethanol was collected in the receiving flask. In the second step, the bis(hydroxypropyl) fumarate was transesterified to afford PPF and ethanol as the primary by-product. This reaction was carried out under vacuum (<1 mmHg) while the temperature was slowly increased from 100 to 130 °C (increment of 10 °C every 30) until the required molecular weight of PPF was obtained. The crude polymer product was thereafter dissolved in dichloromethane (DCM) and the reaction mixture was washed twice with a 1.85% $^{v}/_{v}$ solution of HCl to remove the catalyst. Thereafter the purification step was repeated with doubled-distilled water and portions of brine solution respectively. The organic phase was dried over anhydrous sodium sulphate, filtered and DCM was removed by rotary evaporation. The resulting polymer solution was poured into a previously chilled diethyl ether solution for removal off excess hydroquinone by precipitation of the purified PPF. Subsequently, the precipitate was isolated and re-suspended in DCM which was also removed under vacuum to yield the pure PPF polymer (Shung et al., 2002; Kasper et al., 2009; Timmer et al., 2003; Shulin et al., 2000).

2.3. Copolymer blend to form the pseudo-bone thermo-gel

a) Preparation of Copolymer Blend by Free Radical Polymerization

The copolymer blend was synthesized by free radical polymerization of ε-caprolactone using PEG (Mw 4000) as the macro

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