



Design of chitospheres loaded with pristine polymer particles for extended drug delivery via polyelectrolyte complexation and particulate leaching



Poornima Ramburrun, Yahya E. Choonara, Pradeep Kumar, Lisa C. du Toit, Viness Pillay*

Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, 7 York Road, Parktown, 2193, South Africa

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ABSTRACT

The aim of this study was to investigate the drug release from swellable chitospheres laden with pristine polymethylmethacrylate (PMMA) nanoparticles. Chitosan matrices were prepared by sodium tripolyphosphate crosslinking from a chitosan suspension containing the model BCS class II drug, indomethacin. PMMA particles were added to the chitospheres as the modulator for drug release. Swelling and erosion studies in conjunction with textural profiling provided an understanding of the dominant and underlying drug release mechanisms of the ionically crosslinked chitospheres loaded with the pristine PMMA particles. A series of drug release studies performed in PBS pH 7.4 showed that the pristine particle-loaded chitospheres released indomethacin over 144 h in a first-order manner with 50% drug release occurring over 48 h. The study also revealed that *in situ* porogen leaching for pore creation and polyelectrolyte complex formation were the main mechanisms of release from the chitospheres. The results of this study may be utilized for the development of neuro-implants for controlled delivery of bioactives to the brain where scaffolds of superior mechanical strength and reduced swelling properties are required.

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1. Introduction

Chitosan matrices, particularly spheres, formed from ionotropic and covalent crosslinking has long been used as a three-dimensional matrix for the study of release profiles of numerous drugs with the intent to modulate drug release profiles in a manner that provides drug release of kinetic order and therapeutic effectiveness (Gupta and Ravi Kumar, 2000; Mi et al., 2003; Sarkar et al., 2013). These multiparticulate spherical matrices (Pasparakis and Bouropoulos, 2006; Srinatha et al., 2008; Kotadiya et al., 2009; Yang et al., 2011; Ko et al., 2002; Lin et al., 2005; Harris et al., 2010; Jonassen et al., 2012; Rampino et al., 2013) comprise chitosan alone or blended with other property-modifying natural or synthetic polymers that have been widely used for the oral delivery of therapeutic agents and for long-term sustained delivery of proteins, peptides and other essential growth factors for tissue regeneration applications and gene delivery technologies (Anal et al., 2003; Vimal et al., 2013).

Chitosan is readily soluble in acidic pH, with the resultant protonated amine group available for ionic interaction with multivalent ions for immediate gelation (Jonassen et al., 2012; Shenvi et al., 2014). The cationic nature of chitosan also makes it simple for producing physically crosslinked gelling matrices and the ability to electrostatically interact with counter ionic polymers to form polyelectrolyte complexes (PECs) (Cerf et al., 2014; Nath et al., 2015). Previously reviewed PEC applications show that PECs have unique physicochemical and mechanical properties to that of the parent polymers and offer an additional dimension to the delivery system and enhanced properties for tailoring drug release patterns to the desired site (Hamman, 2010). Sodium tripolyphosphate (STPP) has been frequently used as an ionic crosslinking agent for chitosan matrices due to its rapid crosslinking action and safety compared to glutaraldehyde, epichlorohydrin and ethylene glycol diglycidly ether that have proven physiological toxicity (Mi et al., 1999; Shu and Zhu, 2002; Li and Huang, 2012; Shenvi et al., 2014). Chitosan-based multiparticulates can instantly be synthesised using STPP which forms either intermolecular or intramolecular linkages that stabilize the positively charged amino groups of chitosan resulting in crosslinking (Mi et al., 1999, 2003). Previous studies, aiming to extend the release of indomethacin from crosslinked chitosan and other

* Corresponding author. Tel.: +27 11 717 2274; fax: +27 11 642 4355/86 553 4733.
E-mail address: viness.pillay@wits.ac.za (V. Pillay).

multiparticulate systems over 12–24 h have been reported (Mi et al., 2002; Yuksel et al., 2011). However, the poor mechanical strength of these matrices limits its use in the pharmaceutical industry and the prolonged release of drug and loading efficiency still needs to be improved (Shu and Zhu, 2000). Strategies aimed at improving mechanical strength of and more particularly the controlled release of drug from chitosan beads includes the use of genipin as a covalent crosslinker as opposed to ionic crosslinkers. Yang et al. (2011) investigated the mechanical properties of STPP/genipin co-crosslinked chitosan beads whereas Harris et al. (2010) employed a series of chitosan hydrochloride genipin crosslinking reactions for the controlled release of drugs and proteins. Another widespread method employed for enhancing the drug delivery properties of chitosan beads involve the polyelectrolyte complexation of chitosan with anionic polymers either via blending of polymers prior to bead formation or coating of the beads employing a series of layering techniques using mainly alginates (Wang et al., 2010; Gong et al., 2011; Zhang et al., 2011; Torelli-Souza et al., 2012; Zhou et al., 2013) and pectins (Maestrelli et al., 2012; Ribeiro et al., 2014).

Therefore, the present study makes use of chitospheres to investigate drug release profiles when pristine (previously unmodified and drug-free) polymer nanoparticles of a polymethyl methacrylate (PMMA) polymer are distributed throughout the matrix. The electrostatic interaction between the native polymers producing the PEC can significantly improve the mechanical properties, particularly resilience and hardness, in addition to prolonging drug release.

The use of PMMA is to control drug release from the chitospheres. PMMA (as the pristine nanoparticles) is an anionic copolymer of polymethacrylic acid and methyl methacrylate (Eudragit S100, Evonik, Midrand, Gauteng, South Africa). PMMA is soluble at a pH value of >7.0 and electrostatic interactions between anionic PMMA and cationic chitosan may assist in prolonging drug release. Incorporating it as pristine particles within the chitospheres allows the PMMA to function as a porogen and simultaneously form a PEC after the pH-responsive dissolution of the particles. This technique of inducing porosity and PEC formation holds promise for improving matrix resilience and extending drug release as the matrix undergoes hydration. Such PECs between chitosan and polymethacrylate copolymers are possible and have been previously confirmed where polymethacrylates, in solubilised solution form, were used as surface coating agents for pH-controlled release of entrapped drugs (Lorenzo-Lamosa et al., 1998; Moustafine et al., 2008; Hamman, 2010). A PEC was inadvertently formed at the PMMA film-chitosan bead interface upon coating, however the primary use of the PMMA coating was for its gastro-protective and enteric drug-releasing properties. To our knowledge, this is the first report of *in situ* polyelectrolyte synthesis in addition to *in situ* porogen leaching. The anti-inflammatory drug, indomethacin, is a BCS class II drug with good permeability and poor aqueous dissolution that limits its bioavailability (Obitte et al., 2014). Transition changes of indomethacin from crystalline to amorphous states within the loaded chitospheres may potentially improve its solubility and hence enhance bioavailability (Yuksel et al., 2011; Priemel et al., 2013). Such changes induced within the chitospheres by addition of PMMA and its pH-responsive dissolution may significantly prolong drug release.

The aim of this study was to determine the mechanistic interactions of PMMA as pristine particles with chitospheres and evaluate its modulating ability to prolong drug release in comparison to conventional chitosan spheres. This work involved the preparation of the chitospheres via ionotropic gelation in order to investigate the shift in drug release profiles induced by the incorporation of PMMA pristine particles in varying ratios. Analysis

of the drug release profiles using non-linear kinetic modelling and the corroboration thereof with further characterisation such as SEM imaging, textural profiling, swelling and erosion studies were undertaken in order to determine the mechanisms governing drug release from the modified chitospheres.

2. Materials and methods

2.1. Materials

Chitosan (Poly D-glucosamine, deacetylated chitin, medium molecular weight), indomethacin (>99% TLC), sodium tripolyphosphate (technical grade, 85%) and dialysis tubing cellulose membrane (molecular weight cut-off = 14,000 Da) were purchased from Sigma Aldrich Co. (St. Louis, MO, USA). Eudragit S100 was purchased from Evonik (Midrand, Johannesburg, South Africa) and was used without further modifications as the pristine PMMA particles. Acetic acid glacial (98.5%) and ethanol (99% absolute) were purchased from AceChem (Johannesburg, Gauteng, South Africa) and LabChem (Edenvale, Gauteng, South Africa) respectively. Millipore water was used for all the preparations.

2.2. Synthesis of chitospheres

Chitospheres were prepared by the conventional method of ionotropic gelation, adapted from Bodmeier, et al. (1989) and Shu and Zhu (2000), using STPP as the ionic crosslinking agent. A 2% w/v chitosan solution was prepared by dissolving chitosan in 1 M acetic acid at room temperature until homogenous. The model drug, indomethacin (1% w/v) was dissolved in pure ethanol and added to the chitosan solution. After evaporation of ethanol, PMMA (as the pristine PMMA nanoparticles), was added to the chitosan-indomethacin solutions in the following ratios of chitosan to pristine PMMA particles: 2:1, 1:1 and 1:2 (Table 1). This produced a homogenous distribution of drug throughout the polymer solution. Multiparticulates from a chitosan-indomethacin solution were prepared without the addition of pristine PMMA particles as a control formulation. The indomethacin loaded chitosan-PMMA particle suspensions were then dropped through a 21 gauge hypodermic needle at a flowrate of 0.4 mL/min into STPP crosslinking solutions of 1%, 2% and 3% w/v to form chitospheres. The chitospheres were left to cure in the crosslinking solutions for 30 min (Mi et al., 1999; Shu and Zhu, 2000, 2002) before being separated, washed and collected. The chitospheres were washed with 1 M acetic acid to remove excess drug and any uncrosslinked chitosan from the surface. The chitospheres were then dried at 50 °C for 48 h and stored in a desiccator before further physicochemical characterization and drug-release profiling.

Table 1

List of chitospheres prepared with different concentration ratios of chitosan and PMMA.

STPP crosslinking	Chitosan: pristine PMMA particles ratio w/w
1%	Control (chitosan only)
	2:1
	1:1
	1:2
2%	Control
	2:1
	1:1
	1:2
3%	Control
	2:1
	1:1
	1:2

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