Swellable Microparticles as Carriers for Sustained Pulmonary Drug Delivery

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Received 16 July 2009; revised 20 September 2009; accepted 29 September 2009

Published online 4 December 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22003

ABSTRACT: In this investigation, novel biodegradable physically crosslinked hydrogel microparticles were developed and evaluated *in vitro* as potential carriers for sustained pulmonary drug delivery. To facilitate sustained release in the lungs, aerosols must first navigate past efficient aerodynamic filtering to penetrate to the deep lung (requires small particle size) where they must then avoid rapid macrophage clearance (enhanced by large particle size). The strategy suggested in this study to solve this problem is to deliver drug-loaded hydrogel microparticles with aerodynamic characteristics allowing them to be respirable when dry but attain large swollen sizes once deposited on moist lung surfaces to reduce macrophage uptake rates. The microparticles are based on PEG graft copolymerized onto chitosan in combination with Pluronic® F-108 and were prepared via cryomilling. The synthesized polymers used in preparation of the microparticles were characterized using FTIR, EA, 2D-XRD, and differential scanning calorimetry (DSC). The microparticles size, morphology, moisture content, and biodegradation rates were investigated. Swelling studies and *in vitro* drug release profiles were determined. An aerosolization study was conducted and macrophage uptake rates were evaluated against controls. The microparticles showed a respirable fraction of approximately 15% when prepared as dry powders. Enzymatic degradation of microparticles started within the first hour and about 7–41% weights were remaining after 240 h. Microparticles showed sustained release up to 10 and 20 days in the presence and absence of lysozyme, respectively. Preliminary macrophage interaction studies indicate that the developed hydrogel microparticles significantly delayed phagocytosis and may have the potential for sustained drug delivery to the lung. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:2343–2356, 2010
Keywords: drug delivery; chitosan; PEG; microparticles; pulmonary; lung; inhalation therapy; hydrogels; sustained drug release

INTRODUCTION

The last few years have witnessed a great interest in studying the delivery of therapeutic molecules administered by pulmonary route for both local and systemic treatments. This great deal of attention is due to the numerous advantages of pulmonary drug delivery over many other delivery routes. These advantages include the large alveolar surface area suitable for drug absorption, low thickness epithelial barrier, extensive vascularization, and the relatively low enzymatic metabolic activity in addition to the absence of the first-pass effect.[1–3]

However, due to the efficiency of local clearance mechanisms, designing a respirable carrier system with adequate aerodynamic properties that can confer sustained release of drug once deposited in lung is considered one of the major challenges in pulmonary drug delivery.[3,4] Particles, targeted to the deep lung, should be small enough (0.5–5 μm aerodynamic diameters) to pass through the mouth, throat, and conducting airways and reach the deep lung, but not so small (<0.5 μm) that they fail to deposit and are exhaled again.[4] Understandably from an evolutionary and pulmonary toxicology perspective, microparticles of these sizes have rapid clearance from lung by alveolar macrophages. Increasing microparticle size has been shown to reduce macrophage phagocytosis;[5,6] however, increasing particle size is unpractical for pulmonary drug delivery purposes due to the efficient filtering role performed by the upper airways. Therefore,

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Journal of Pharmaceutical Sciences, Vol. 99, 2343–2356 (2010)
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development of swellable microparticles that have respirable aerodynamic sizes when dry but, upon deposition in the lung, attain larger geometric sizes via controlled swelling to avoid macrophage clearance represents a very promising strategy. In these studies, we designed respirable hydrogel microparticles based on chitosan (Cs), poly(ethylene glycol) (PEG), and Pluronic® polymer systems.

Cs [a (1→4)2-amino-2-deoxy-β-D-glucan] is a cationic biopolymer obtained through alkaline *N*-deacetylation of natural chitin. Cs has numerous desirable properties such as biodegradability, nontoxicity, and biocompatibility.[7–9] It has been reported also that Cs has many advantageous characteristics for improving drug absorption, such as protection of the drug against enzymatic degradation[10] and absorption-enhancing effects in both GI tract[11,12] and nasal mucosa.[13,14] Recently, it has been confirmed also that Cs has a significant drug absorption-enhancing effect in the pulmonary tissues.[15] It was suggested that the absorption-enhancing mechanism of Cs in lung tissues might be due to transient opening of the intercellular tight junction of the lung epithelium, which is the same mechanism already reported for intestinal and nasal mucus membranes.[15] Moreover, the reactive amino groups in the backbone of Cs make it possible to chemically conjugate various molecules, which may improve performance of the delivery system.[16,17] These characteristics make Cs an ideal candidate in the preparation of hydrogel carriers for controlled drug release.[16–18]

PEG is a highly water-soluble polymer. Due to the high hydrophilicity, lack of toxicity and biocompatibility of PEG, grafting of it onto Cs is considered to be a convenient route to synthesize drug carriers with desirable features.[19] In addition, it has been widely shown that PEG coating on micro and nanoparticles leads to decreased macrophage engulfment.[5] Of different polymeric carriers based on Cs derivatives with improved hydrophilicity, nanosized hydrogel particles based on PEG graft copolymerized onto Cs have received recently a growing interest as novel potential carriers for drugs.[20–26]

Pluronics® is a class of biocompatible water-soluble triblock copolymers (also known as "poloxamers"). These block copolymers consist of hydrophilic poly (ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) blocks arranged in A–B–A triblock structure: PEO-*b*-PPO-*b*-PEO.[27] Pluronics® have found widespread use for many biomedical applications. These include cell encapsulation[28] and coatings for medical devices.[29] Also, Pluronics® have been used in drug delivery systems such as hydrogels and micelles[30,31] that are FDA approved. The main feature of these polymers is their amphiphilic character, which enables them to display surfactant properties including ability to interact with hydrophobic surfaces and biological membranes. In addition, this amphiphilic nature is a reason for success of Pluronics® in drug delivery as it allows the solubilization of hydrophobic drugs in an aqueous environment and increases drug stability and also improves the drug pharmacokinetics and biodistribution.

In this study, novel biodegradable physically crosslinked (amphiphilic interactions) hydrogel microparticles were developed and evaluated *in vitro* as potential carriers that can confer pulmonary sustained drug delivery. These hydrogel microparticles were prepared to show desired respirable aerodynamic size when dry but large swollen size when deposited in the lung to avoid macrophage clearance. The microparticles are based on PEG graft copolymerized onto Cs in combination with Pluronic® F-108 and were prepared in mild conditions via cryomilling. To the best of our knowledge, these are the first studies to investigate swellable microparticles for pulmonary drug delivery.

MATERIALS AND METHODS

Materials

Monomethoxy-poly(ethylene glycol) (m-PEG, Mn 5000 Da), Cs (medium MW, % *N*-deacetylation; about 76.4%, as determined by elemental analysis), succinic anhydride and 1-hydroxybenzotrizole (HOBt) were purchased from Aldrich, St. Louis, MO. Pluronic® F-108 Pastille was obtained from BASF, Chattanooga, TN Corporation. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCL) was purchased from Fluka Chemical Corp (Milwaukee, WI). 4-Dimethylaminopyridine (DMAP) was provided by Sigma, St. Louis, MO. Phthalic anhydride, sodium fluorescein (SF), triethyl amine, hydrazine monohydrate, dioxane, and dimethyl formamide (DMF) were obtained from Sigma–Aldrich, St. Louis, MO, SIAL. Lactose excipient (Respitose® ML001 was obtained from DMV-Fonterra Excipients (Goch, Germany). Phosphate-buffered saline (PBS, pH 7.4) and all other reagents were of analytical grade and used as received.

Methods

Synthesis of PEG-Cs Graft Copolymer

The copolymer of m-PEG macromer grafted onto Cs was prepared by a modified method to that reported by Yoksan et al.[32] and Yoksan and Chirachanchai.[33] The synthesis sequence was as follows.

Firstly, the free NH_2 groups of Cs were protected via *N*-phthaloylation. In brief, 10 g Cs was reacted with phthalic anhydride (44.8 g, 5 mol equivalent

 DOI 10.1002/jps

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