International Journal of Pharmaceutics 481 (2015) 1–8

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

A charge neutral, size tuneable polymersome capable of high biological encapsulation efficiency and cell permeation

Chloe Martin, Elsa Dolmazon, Katrina Moylan, Colin Fowley, Anthony P. McHale, John F. Callan, Bridgeen Callan *

School of Pharmacy and Pharmaceutical Sciences, The University of Ulster, Northern Ireland BT52 1SA, United Kingdom

ARTICLE INFO

Article history:
Received 3 November 2014
Received in revised form 19 December 2014
Accepted 26 December 2014
Available online 12 January 2015

Keywords:
Drug delivery
Drug release
Fluorescence
Hydrophilicity
Polymersome
Polymerisation

ABSTRACT

The field of therapeutics is evolving to include a greater proportion of higher molecular weight, hydrophilic biological compounds. To cater for this new era in healthcare the concomitant development of appropriate drug delivery systems is essential to aid cellular permeation. In this manuscript we present the synthesis, characterisation and biological evaluation of a charge neutral polymersome (Ps) based drug delivery system (DDS) using an amphiphilic pegylated random copolymer. A detailed dynamic light scattering study revealed that the hydrodynamic diameter of the Ps can be tailored to a specific size simply by varying the quantities and ratios used during the preparation step. The zeta potential of this new drug delivery system was determined to be -0.095 ± 0.037 mV, the encapsulation efficiency of Fitc-CM-Dextran (4 KDa) was 70%, the uptake of Fitc-CM-Dextran by Hela cells was increased 4-fold when encapsulated within the polymersomal system. The facile preparation, high loading capacity and size tuneable nature of this Ps renders it a promising alternative to the ever growing array of currently available Ps.

1. Introduction

Medicine has evolved from the 'one size fits all' approach to drug development with thanks in part to the Human Genome Project (HGP) that was completed more than a decade ago (Consortium, 2001). Since the completion of this landmark discovery there has been a pervasive increase and exploration of personalised medicine. The therapeutic use of siRNAs, proteins and enzymes has allowed for a revolution in healthcare regimes (Guo et al., 2010). In order to reach its full potential, it is essential that these therapeutics can be delivered to the required site of action. These large, hydrophilic and often highly charged compounds come with their own problems regarding cell permeability and drug delivery. One method that has proven successful for the delivery of these biological compounds is the use of nanoparticles (NPs). NPs are colloidal nano-sized particles with a diameter ranging between 1 and 1000 nm whereby the drug of interest can either be encapsulated, absorbed or dispersed within them (Allen and Cullis, 2013; Mazak and Noszal, 2014; Vonarbourg et al., 2006). Nanoparticulate systems show promise as active vectors due to their capacity to release drugs, subcellular size allowing for relatively high intracellular uptake, the potential to provide improved stability of active substances and their biocompatibility with tissues and cells (Mora-Huertas et al., 2010). A wide variety of nanoparticles composed of a range of materials have been developed, resulting in delivery systems that vary in their physicochemical properties and thus their applications (Burt and Letchford, 2007). Current nanoparticulate drug delivery systems being investigated include liposomes (Qu et al., 2014), micelles (Torchilin, 2007), nanospheres (Yu et al., 2014), nanocapsules (Musyanovych and Landfester, 2014), niosomes (Kazi et al., 2010) and polymersomes (Wang et al., 2014; Discher et al., 1999; Levine et al., 2008; Ahmed et al., 2006) among others.

Currently there are several liposomal based drug delivery systems approved by the U.S. food and drug administration. Although these formulations show enhanced delivery and efficacy of therapy, they still have been shown to render some serious side effects (Nahire et al., 2014), partially due to their surface charges (Barenholz, 2012). To that end we have developed a polymersomal based drug delivery system that is charge neutral and whose hydrodynamic diameter can be tailored according to the desired size of the nanoparticle required.

Polymersomes are polymeric capsules with a bilayered membrane comprised of synthetic amphiphilic block copolymers,

* Corresponding author. Tel.: +44 28 70 123510; fax: +44 28 70 123518.
E-mail address: b.callan@ulster.ac.uk (B. Callan).

http://dx.doi.org/10.1016/j.ijpharm.2014.12.061
0378-5173/

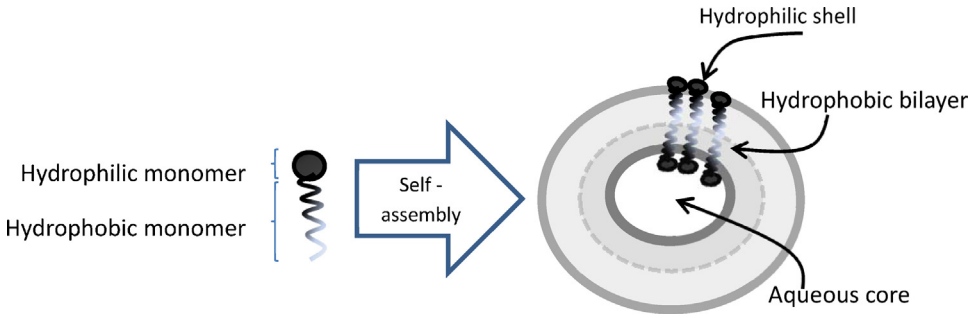


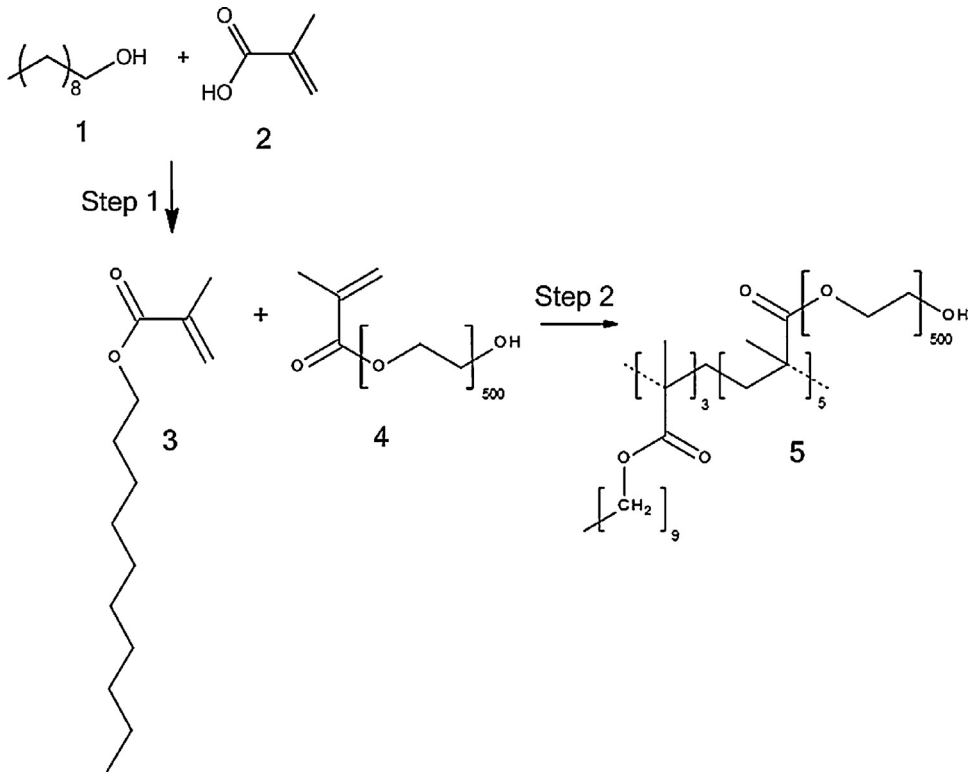
Fig. 1. Schematic representation of polymersome formed from amphiphilic co polymer.

Fig. 1. Their macromolecular structure is similar to that of the liposome in that they are both composed of a bilayer of amphiphiles enclosing an aqueous compartment (Brinkhuis et al., 2011). However, the difference between these two vehicles is that most liposomes are naturally occurring phospholipids and as such have both a strong negative charge and lower molecular weight than the synthetic polymeric alternatives. This enhanced ability to specifically tailor Ps formulation methods, physicochemical properties, release mechanisms and even targeting chemistries make polymersomes an ideal platform for the encapsulation of a broad range of therapeutic molecules (Christian et al., 2009). The incorporation of poly(ethylene glycol) (PEG) as the hydrophilic component in many of these polymersomal NPs is commonplace as it has been shown to reduce the reticuloendothelial system (RES) uptake as well as to increase the circulation time of the NP (Jokerst et al., 2011). Here we present for the first time a neutral, size tuneable Ps prepared from a co-polymer we have previously shown to self-assemble and form a micellar structure capable of encapsulating hydrophobic drugs and successfully permeate cell membranes (Yildiz et al., 2011). The random co-polymer consists of hydrophilic (PEG) and hydrophobic counterparts (decyl chain) (Scheme 1). We have formulated this neutral co-polymer into a polymersomal drug delivery system (Ps DDS) capable of encapsulating Fitc-CM-Dextran (MW 4 KDa) with high efficiency as well as having the ability to 'fine tune' the diameter of the vehicle as required. Fitc-CM-Dextran has been utilised as a surrogate for siRNA as it is an anionic fluorescent dextran that can be used as a biological mimic, due to its high molecular weight and hydrophilicity. When tested in Hela cells the Ps showed a 4-fold increase in uptake of Fitc-CM-Dextran compared to cells treated with Fitc-CM-Dextran alone.

2. Materials and methods

2.1. Materials and reagents

Chemicals were purchased from commercial sources at the highest possible purity and used as received. Poly(ethylene glycol)



Scheme 1. Synthesis of monomer **3** (step 1) and production of co polymer **5** (step 2).