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Polyurethane and polyurea nanoparticles based on polyoxyethylene castor oil derivative surfactant suitable for endovascular applications

Genoveva Morral-Ruíz [a], Pedro Melgar-Lesmes [a], María Luísa García [b], Conxita Solans [c,d], María José García-Celma [a,d,*]

[a] Departament de Farmàcia i Tecnologia Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona, Av Joan XXIII s/n, 08028 Barcelona, Spain
[b] Departament de Fisicoquímica, Facultat de Farmàcia, Universitat de Barcelona, Av Joan XXIII s/n, 08028 Barcelona, Spain
[c] Institut de Química Avançada de Catalunya (IQAC), CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain
[d] Networking Research Center on Bioengineering, Biomaterials and Nanomedicine, CIBER-BBN, Barcelona, Spain

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ABSTRACT

The design of new, safe and effective nanotherapeutic systems is an important challenge for the researchers in the nanotechnology area. This study describes the formation of biocompatible polyurethane and polyurea nanoparticles based on polyoxyethylene castor oil derivative surfactant formed from O/W nano-emulsions by polymerization at the droplet interfaces in systems composed by aqueous solution/Kolliphor® ELP/medium chain triglyceride suitable for intravenous administration. Initial nano-emulsions incorporating highly hydrophilic materials were prepared by the phase inversion composition (PIC) method. After polymerization, nanoparticles with a small particle diameter (25–55 nm) and low polydispersity index were obtained. Parameters such as concentration of monomer, O/S weight ratio as well as the polymerization temperature were crucial to achieve a correct formation of these nanoparticles. Moreover, FT-IR studies showed the full conversion of the monomer to polyurethane and polyurea polymers. Likewise the involvement of the surfactant in the polymerization process through their nucleophilic groups to form the polymeric matrix was demonstrated. This could mean a first step in the development of biocompatible systems formulated with polyoxyethylene castor oil derivative surfactants. In addition, haemolysis and cell viability assays evidenced the good biocompatibility of KELP polyurethane and polyurea nanoparticles thus indicating the potential of these nanosystems as promising drug carriers.

1. Introduction

The design of new therapeutic systems based on nanostructured carriers for controlled drug delivery has undergone a boost in the last years (Beija et al., 2012; Peer et al., 2007; Parveen et al., 2012; Elzoghby et al., 2012). In particular, among the numerous developed colloidal systems (Beija et al., 2012; Johnston et al., 2011; Sahoo and Labhasetwar, 2003; Immordino et al., 2006), polymeric nanoparticles constitute a promising therapeutic tool owing to their unique key features such as high kinetic stability, wide structural variety and rigid morphology (Anton et al., 2008). Nanoparticles have been traditionally defined as solid colloidal materials built from macromolecular or molecular assemblies with a diameter in the range of 1–500 nm (Kreuter, 2004). Therefore, one of the main challenges in the formation of nanoparticles for drug delivery is the right choice of the polymer since this will determine the final properties of the colloidal system and consequently the administration route (Anton et al., 2008). In this context, polyurethane and polyurea polymers have focused a growing interest as emergent biomaterials for endovascular applications due to their synthetic versatility, excellent mechanical properties and good biocompatibility (Laschke et al., 2009; Hong et al., 2012; Page et al., 2012). These materials are usually synthesized from the polycondensation or polyaddition reaction of diisocyanates and alcohol or amine groups (Ionescu, 2005). Cremophor® EL is a polyoxyethylene castor oil derivative surfactant which posses free hydroxyl groups in its chemical structure that has been extensively used as pharmaceutical vehicle for several anaesthetics, analgesics, antineoplastic and immunosuppressive drugs in numerous oral and parenteral delivery systems (Csóka et al., 1997; Venkata Ramana Rao and Saho, 2008). Although its intravenous application is currently approved by the US Food and Drug Administration and the European Medicines Agency, it is not a completely inert compound and can generate acute hypersensitivity reactions in susceptible patients (Ten Tije et al., 2003; Theis et al., 1995). It has

* Corresponding author at: Av Joan XXIII s/n, 08028 Barcelona, Spain. Tel.: +34 934024548; fax: +34 934035937.
E-mail address: mjgarcia@ub.edu (M.J. García-Celma).

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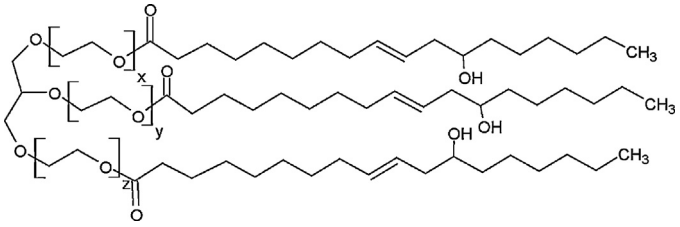
been reported that this adverse effect could be attributed to the presence of nucleophilic groups in the hydroxyl-polyethoxylene segments of the surfactant which are able to trigger the complement activation (Weiszhár et al., 2012). Therefore, the formation of polyurethane polymers profiting hydroxyl groups of the surfactant could mean an important advance on the development of drug delivery systems based on Cremophor® EL and other similar surfactants since their reactive groups would be blocked and unable of activating the blood complement proteins. On the other hand, intravenous administration requires that nanotherapeutics remain in the blood stream time enough to reach the target cell, organ or tissue. Thereby, it is important that these systems exhibit stealth properties for not being quickly recognized and removed from the organism by the action of the reticuloendothelial system (RES). In this regard, it is well known that an increase of the hydrophilicity of the colloidal system as well as a small particle size (under 100 nm) can considerably decrease the RES uptake thus improving the circulation times in blood (Weiszhár et al., 2010; Vonarbourg et al., 2006). Considering that both properties are bind up with the preparation method of the colloidal system, the selection of a suitable method will be also crucial to develop nanoparticles for endovascular applications. Among the many novel techniques developed to date (Zhang et al., 2005; Kim et al., 2009; Moch et al., 2006; Rao and Geckeler, 2011), the formation of nanoparticles from O/W nano-emulsions provides important advantages regarding to other methods since it allows not only obtaining nanocarriers with the desired particle size and low polydispersity but also the formation of a broad range of functionalized polymeric structures (Anton et al., 2008; Landfester, 2006; Holzapfel et al., 2005). Although several studies have described the formation of polyurethane and polyurea nanoparticles by mechanisms of polymerization in nano-emulsions, these systems have been mainly obtained by high-energy methods (Zanetti-Ramos et al., 2006; Tiarks et al., 2001; Johnsen and Schmid, 2007). Although these methods have been well proven and repeatable, it should be mentioned that they require an extra energy input which is usually provided from mechanical devices such as high-shear stirring, high-pressure homogenizers and ultrasound generators to obtain nano-emulsions with a small droplet size and low polydispersity (Solans et al., 2005). In this regard, it is well known that nano-emulsions with the smallest sizes can be obtained using an external device able to supply the required energy in the shortest possible time with the most homogeneous flow (Walstra, 1996).

Nevertheless, nano-emulsions with the desired size and polydispersity properties can be produced almost spontaneously just taking advantage of the chemical potential of the system (low-energy emulsification methods) (Rang and Miller, 1999; Bouchemal et al., 2004). In this regard, it has been reported that nano-emusions with even smaller and more uniform droplet diameters can be achieved by using low-energy methods (Solans et al., 2005; Galindo-Alvarez et al., 2011). These methods include the Phase Inversion Temperature (PIT) method which is based on changing the temperature of the system keeping constant the composition (Izquierdo et al., 2004) and the Phase Inversion Composition (PIC) method, in which phase transitions occur by modifying the composition at constant temperature (Solè et al., 2010).

In the present report we focused our efforts on the design of shell-modified polyurethane and polyurea nanoparticles suitable to be intravenously administered. These nanoparticles were synthesized by interfacial polycondensation from O/W nano-emulsions prepared by low-energy methods in aqueous solution/polyoxyethylene castor oil derivative surfactant/saturated medium chain triglyceride systems. To achieve this aim nanoparticles prepared with highly hydrophilic materials were comprehensively characterized and different parameters implied in the polymerization process were also investigated. Likewise



Scheme 1. Molecular structure of Polyoxyl-35-castor oil (Kollipohor®ELP) where $x+y+z=35$.

biocompatibility studies were also performed. In this context, special attention was focused on the involvement of surfactant in the polymerization reaction in order to achieve the inactivation of nucleophilic groups which have been bond up with the appearance of acute hypersensitivity reactions in susceptible patients. Thus, our studies could mean a great step forward to develop systems with polyoxyethylene castor oil derivative surfactant with a good biosafety profile and efficiency.

2. Experimental

2.1. Materials

The nonionic technical grade surfactant, Kolliphor® ELP (KELP) was a gift from BASF (Ludwigshafen, Germany). This component is a purified polyoxyethylene castor oil derivative surfactant with free hydroxyl groups in its chemical structure, which is synthesized by reacting castor oil with ethylene oxide in a molar ratio of 1:35. The hydrophobic fraction comprises about 83% of the total mixture, being the glycerol polyethylene glycol ricinoleate the main component. On the other hand, the hydrophilic part (corresponding to the other 17 wt%) consists of free polyethylene glycols and glycerol ethoxylates (Singh, 2009). The molecular structure of this surfactant is shown in Scheme 1. Due to its hydrophilic–lipophilic balance (HLB) which lies between 12 and 14 (BASF Corporation, Technical Literature), KELP is a good choice to obtain O/W nano-emulsions by the phase inversion composition method. Regarding to its solubility, KELP is soluble in water at 25 °C forming direct micelles at a surfactant concentration of 0.02 wt% (critical micelle concentration). However the solubility of the surfactant in water decreases at higher temperatures and the solution becomes turbid (Singh, 2009).

The other components with highly reactive groups, polyethylene glycol 400 (PEG 400) and L-lysine (lys) as well as the monomer, isophorone diisocyanate (IPDI), were purchased from Sigma–Aldrich (St. Louis, MO). The oily component, saturated medium chain triglyceride (MCT) was supplied from Fagron (Barcelona, Spain). All chemicals were used without further purification. Water to prepare different formulations was deionized by Millipore-Milli-Q water purification system (Molsheim, France).

The materials employed in haemocompatibility studies, pig and human blood were obtained from AbD Serotec (Raleigh, NC, USA).

Finally, the primary human endothelial cells HUVECs (Human umbilical vein endothelial cells), Dulbecco's Modified Eagle Medium (DMEM), Ham's F-12 Nutrient Mix (F-12), foetal calf serum (FCS), penicillin/streptomycin antibiotic and endothelial cell growth supplement were purchased from Life Technologies Ltd. (Paisley, UK).

2.2. Methods

2.2.1. Preparation of O/W nano-emulsions

O/W nano-emulsions were prepared at 25 °C by the Phase Inversion Composition (PIC) emulsification method as reported