International Journal of Pharmaceutics 496 (2015) 1034–1046

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Skin delivery by block copolymer nanoparticles (block copolymer micelles)

Faiza Laredj-Bourezg[a], Marie-Alexandrine Bolzinger[a], Jocelyne Pelletier[a], Jean-Pierre Valour[a], Marie-Rose Rovère[b], Batoule Smatti[c], Yves Chevalier[a,*]

[a] Université Lyon 1, Laboratoire d'Automatique et de Génie des Procédés, CNRS UMR 5007, 43 bd 11 Novembre, 69622 Villeurbanne, France
[b] Université Lyon 1, Laboratoire des Substituts Cutanés, CNRS FRE 3310, Hôpital Édouard Herriot, Lyon, France
[c] Université Lyon 1, Centre d'Imagerie Quantitative Lyon-Est, Lyon, France

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 12 November 2015
Accepted 14 November 2015
Available online 19 November 2015

Keywords:
Skin delivery
Cutaneous absorption
Block copolymer
Nanoparticle

ABSTRACT

Block copolymer nanoparticles often referred to as "block copolymer micelles" have been assessed as carriers for skin delivery of hydrophobic drugs. Such carriers are based on organic biocompatible and biodegradable materials loaded with hydrophobic drugs: poly(lactide)-*block*-poly(ethylene glycol) copolymer (PLA-*b*-PEG) nanoparticles that have a solid hydrophobic core made of glassy poly(D,L-lactide), and poly(caprolactone)-*block*-poly(ethylene glycol) copolymer (PCL-*b*-PEG) nanoparticles having a liquid core of polycaprolactone. *In vitro* skin absorption of *all-trans* retinol showed a large accumulation of retinol in *stratum corneum* from both block copolymer nanoparticles, higher by a factor 20 than Polysorbate 80 surfactant micelles and by a factor 80 than oil solution. Additionally, skin absorption from PLA-*b*-PEG nanoparticles was higher by one order of magnitude than PCL-*b*-PEG, although their sizes (65 nm) and external surface (water-swollen PEG layer) were identical as revealed by detailed structural characterizations. Fluorescence microscopy of histological skin sections provided a non-destructive picture of the storage of Nile Red inside *stratum corneum*, *epidermis* and *dermis*. Though particle cores had a different physical states (solid or liquid as measured by ^{1}H NMR), the ability of nanoparticles for solubilization of the drug assessed from their Hildebrand solubility parameters appeared the parameter of best relevance regarding skin absorption.

1. Introduction

Drug delivery to skin aims at either the treatment of skin diseases or at reaching the systemic circulation at a slow rate and prolonged time by means of transdermal administration. In the latter case, the drug should reach the dermis layer that is irrigated by the systemic circulation. In general, the purpose of drug carriers is targeting the drugs to their site of activity. Organic particles made of polyesters have been used since a long time for drug delivery and recognized to modulate skin delivery rates and location, allowing a controlled release of drugs. Either deep skin penetration or accumulation in the *stratum corneum* (SC) and follicular appendages can be favored depending on the type of drug carrier (Bolzinger et al., 2012; Maka et al., 2011; Illel, 1997; Alvarez-Román et al., 2004a,b; Schaefer et al., 1990; Toll et al., 2004). Biocompatible and biodegradable polymer particles are attractive because they can be loaded with hydrophobic drugs and they are recognized as safe for their use as drug carriers in the body. It has been recognized since a long time that the size of such polymer particles was an essential parameter that controlled skin delivery (Schaefer et al., 1990; Rolland et al., 1993; Vogt et al., 2006). Small size gives penetration because nanoparticle may penetrate as such, but also because the area of contact with external medium causes a faster release from the particle suspension to the skin. Particle size is not the sole relevant parameter regarding skin absorption however (Bolzinger et al., 2011).

Block copolymer nanoparticles are such polymer nanoparticles that appeared attractive regarding drug delivery because of their very small size. Their application to drug delivery by means of oral or parenteral administration routes have been reviewed recently (Kwon and Okano, 1996; Gaucher et al., 2005; Torchilin, 2007). The utilization of block copolymer nanoparticles as carriers for skin absorption is quite new. The first report dealing with transdermal delivery by block copolymer nanoparticles was an investigation of polycaprolactone-*block*-poly(ethylene glycol) copolymer nanoparticles loaded with the antihypertensive vasodilator mixnoxidil by Shim et al. (2004). It was shown that skin delivery to hairy guinea

* Corresponding author. Fax: +33 472431682.
E-mail address: chevalier@lagep.univ-lyon1.fr (Y. Chevalier).

http://dx.doi.org/10.1016/j.ijpharm.2015.11.031
0378-5173/

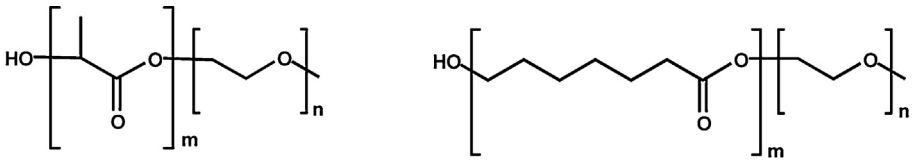
pig skin was larger than to hairless skin, and was dependent on nanoparticle size, suggesting a large contribution of the follicular pathway to the skin absorption. The high potentials of block copolymer nanoparticles for the skin delivery of dermatological drugs have been demonstrated by Bachhav et al. (2011). They showed the improved skin delivery of antifungal drugs by poly (dihexyl lactide)-*block*-poly(ethylene glycol) compared to the commercial o/w emulsion Pevaryl® formulation. Block copolymer liposomes called Polymersomes have also been assessed for skin delivery (Rastogi et al., 2009).

Block copolymer nanoparticles, often called "block copolymer micelles", are such polymer particles of high potential that might improve drug absorption into skin because of their small size in the range 20–100 nm. They are made of amphiphilic block copolymers that are reminiscent of surfactant molecules because they have hydrophilic and hydrophobic parts well-separated in the chemical structure. Their self-assemblies as nanoparticles have the same core–shell structure as the classical surfactant micelles: an internal core made of the hydrophobic blocks is surrounded by a shell made of the hydrophilic blocks swollen by water (Gaucher et al., 2005; Riess, 2003; Gohy, 2005). This is the reason why nanoparticles made of aggregated amphiphilic block copolymers have often been called as "block copolymer micelles". There are actually definite differences between block copolymer micelles and classical micelles made from conventional surfactants. Firstly, strongly amphiphilic block copolymers are not soluble in water whereas conventional micelle-forming surfactants are soluble in water. One first consequence is that there is no *cmc* (critical micelle concentration); or the *cmc* is so low that it cannot be measured (Riess, 2003). The solutions do not contain any free block copolymer molecule. As the second important consequence, the formation of block copolymer micelles is not spontaneous. A preparation process is necessary, which most often involve a solvent shifting method from an organic solution to an aqueous medium. On the contrary, it is well-known that water-soluble surfactant spontaneously self-assemble as micelles when their concentration is higher than the *cmc*. On this basis, the behavior of block copolymer micelles is closer to that of polymer nanoparticles than that of surfactant micelles. In order to discard any confusion, the term "block copolymer micelles" will no longer be used in the paper and the term "block copolymer nanoparticles" will be preferred. Some block copolymers that are less amphiphilic such as the widely used poly(ethylene oxide)/poly(propylene oxide) block copolymers show a surfactant-like behavior with non-vanishing *cmc* values and dynamic partition equilibrium of macromolecules between micelles and their free state in water (Zana et al., 2006); these block copolymer micelles are out of the topic of the present paper.

Block copolymer nanoparticles appear attractive for drug delivery because such micelle-like nanoparticles are able to solubilize hydrophobic drugs and transfer them into the skin; but there are no free block copolymer molecules that might penetrate the skin as in the case of classical surfactant micelles. Classical surfactants are known to cause disorganization of the *stratum corneum* (SC) because of their detergent action and because of their ability to penetrate the SC (Sarpotdar and Zatz, 1987; Cappel and Kreuter, 1991; Ashton et al., 1992a,b; Effendi and Maibach, 1995; López et al., 2000). Both phenomena known as "penetration enhancer effect" (Williams and Barry, 2004, 2012) cause an alteration of the barrier function of the SC. Upon the detergent action of surfactants, the less polar fraction of the lipids in the SC is washed out and the lipid barrier of SC is weakened. Upon their penetration in skin, some surfactants mix with the SC lipids and disorganize the crystalline structure of the intercorneocyte medium, resulting in increased permeability for drug molecules (Ashton et al., 1992a,b). Irritancy is a major issue regarding utilization of surfactants in formulations exposed to the skin surface because of the detergent action that causes water-loss (van der Valk et al., 1984), and because of the intrinsic irritancy behavior of surfactant that manifests in case of their deep penetration in the skin (Effendi and Maibach, 1995). On another hand, the small size of block copolymer nanoparticles might bring about improved skin absorption of hydrophobic drugs compared to classical polymer nanoparticles. Indeed the typical size of block copolymer nanoparticles is 30–50 nm whereas the size-range of polymer nanoparticles is 100–200 nm (Couvreur et al., 1996).

Nanoparticles having a size lower than 100 nm are suspected being hazardous regarding toxicity concerns because their small size allows them to cross biological barriers and penetrate vitally important organs (Monteiro-Riviere and Riviere, 2009; Monteiro-Riviere and Baroli, 2010). There is no such health concern with block copolymer nanoparticles because they are biodegradable (Kumar et al., 2001). In particular poly(lactic acid) and polycaprolactone are major biodegradable polyesters used as materials in pharmaceutical formulations (Edlund and Albertsson, 2002). Neither the block copolymer nor their degradation products are toxic. Such block copolymer nanoparticles are also biocompatible because the PEG hydrophilic shell acts as a protective layer against the immune system (Bazile et al., 1995; Nguyen et al., 2003).

The present study deals with the assessment of skin absorption of hydrophobic drugs loaded in block copolymer nanoparticles. Considering the recent disclosure of the enhanced penetration of antifungal drugs loaded in block copolymer nanoparticles (Bachhav et al., 2011), together with the present observation of a large dependence of skin delivery rates from different types of block copolymer nanoparticles, this study was aimed at investigating the origin of the enhanced skin absorption of hydrophobic drugs and the dependence of block copolymer type. Block copolymer nanoparticles based on either poly(lactic acid) (PLA) or polycaprolactone (PCL) were investigated. The chemical structures of the block copolymers are poly(D,L-lactide)-*block*-poly(ethylene glycol) PLA-*b*-PEG and poly(caprolactone)-*block*-poly(ethylene glycol) PCL-*b*-PEG (Fig. 1). The main difference between PLA and PCL is their physical state since PLA is a solid glassy material whereas PCL is a soft amorphous material (molten polymer) at room temperature. Retinol (vitamin A) was selected as the model



Poly(D,L-lactide)-*block*-poly(ethylene glycol) (PLA-*b*-PEG)

Poly(caprolactone)-*block*-poly(ethylene glycol) (PCL-*b*-PEG)

Fig. 1. Chemical structure of PLA-*b*-PEG and PCL-*b*-PEG block copolymers with polymerization degrees **m** for the hydrophobic (PLA or PCL) block and **n** for the hydrophilic PEG block.