Advances in Colloid and Interface Science 206 (2014) 414–427

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

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

Block copolymers at interfaces: Interactions with physiological media

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ARTICLE INFO

Available online 6 November 2013

Keywords:
Block copolymer
Nanoemulsion
Oil–water interface
Rheology
Lipolysis

ABSTRACT

Triblock copolymers (also known as Pluronics or poloxamers) are biocompatible molecules composed of hydrophobic and hydrophilic blocks with different lengths. They have received much attention recently owing to their applicability for targeted delivery of hydrophobic compounds. Their unique molecular structure facilitates the formation of dynamic aggregates which are able to transport lipid soluble compounds. However, these structures can be unstable and tend to solubilize within the blood stream. The use of nanoemulsions as carriers for the lipid soluble compounds appears as a new alternative with improved protection against physiological media. The interfacial behavior of block copolymers is directly related to their peculiar molecular structure and further knowledge could provide a rational use in the design of poloxamer-stabilized nanoemulsions. This review aims to combine the new insights gained recently into the interfacial properties of block copolymers and their performance in nanoemulsions. Direct studies dealing with the interactions with physiological media are also reviewed in order to address issues relating metabolism degradation profiles. A better understanding of the physico-chemical and interfacial properties of block copolymers will allow their manipulation to modulate lipolysis, hence allowing the rational design of nanocarriers with efficient controlled release.

Contents

1. Introduction and background

Triblock copolymers, also known under their commercial names as Pluronics or poloxamers, have been extensively used in the biomedical

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http://dx.doi.org/10.1016/j.cis.2013.10.027

field as delivery systems [1]. Their versatile molecular structure makes them a promising ingredient for encapsulation and delivery of compounds with different purposes [2]. The structure of triblock copolymers is based on a hydrophobic polyoxypropylene (POP) central block linked to hydrophilic polyoxyethylene (POE) end blocks. The lengths of these blocks can be matched to tune the amphiphilicity of the molecules depending on the specific requirements of the encapsulating agent and administration route [2,3]. However, a main reason for the use of triblock copolymers is their biocompatibility with plasma-derived fluids. For example, the use of block copolymers in gene therapy is a promising area of research [4]. In addition, their biocompatibility has boosted their application in the design of drugs with improved long-circulating properties. Also, they serve as carriers for lipid soluble compounds and more recently, their stabilizing effect is being applied in the development of food products with satiating effects by delaying lipid digestion [5–7].

So far, most of the applications of triblock copolymers are based on their spontaneous self-assembly. Poloxamers can aggregate in aqueous solution building up micelles with a hydrophobic core (POP) and a hydrophilic corona (POE) which can serve as encapsulating system for hydrophobic compounds [8]. These structures are versatile and have been employed for encapsulating different compounds, but still their low stability and several problems associated with the degradation owing to solubilization in the blood stream [1,9] remain a challenge.

An alternative method to face the low stability of the aggregates for drug delivery is the use of nanocarriers. Triblock copolymers are surface active molecules which can hence be used as protective coating for nanocarriers, with the central POP block adsorbed onto hydrophobic interfaces, whereas the two lateral POE chains remain in the hydrophilic phase, forming a steric bulky layer. In this regard, the interfacial structure of triblock copolymers provides a protective effect under intravenous conditions which is determinant for the performance of the encapsulation and controlled release [10].

Hence, an emerging application of block copolymers is to extend their functionality to stabilize oil-in-water emulsions as drug delivery systems [11,12]. We will focus in the use of nanoemulsions as delivery systems, which is gaining interest in the pharmaceutical industry [13]. Nanoemulsions were first developed with the aim of helping patients to overcome a critical nutrition state (patients in intensive care or in convalescence) by providing them with triglycerides by parenteral route. In recent years, development has continued into more innovative emulsion formulations, e.g. varying the emulsified oil and/or the emulsifiers [10]. The combination of the advantages of traditional parenteral emulsions (mainly biocompatibility and biodegradability) with the new functionalities has led to the first marketed drug delivery systems based on nanoemulsions [14]. The main advantages of nanoemulsions in the field of drug delivery systems for hydrophobic drugs are: inexpensive and easy-to-scale production, low toxicity, independence of dilution and reduced side effects [13].

The ultimate goal of a drug delivery system is to deliver the encapsulated compound at the right time in a safe and reproducible manner. An ideal drug delivery system should transport the drug to the targeted organ or receptor in the required dose, preserving it intact after crossing the different physiological barriers [15,16]. In the case of nanoemulsions, the accessibility of the lipid will ultimately control the release and degradation profile of the drug [17]. Therefore, lipid digestion is the limiting step in these systems and should be importantly accounted for in the manufacture. Lipid digestion mainly takes place in the duodenum where different surface active systems exist: the enzyme pancreatic lipase and its cofactor colipase, and bile salts (BS). BS are natural surfactants which adsorb onto oil–water interfaces in food emulsions, displacing any other surface active system and hence preparing the interface for the adsorption of the lipase–colipase complex [18]. Once lipase reaches the oil–water interface, the lipid digestion or lipolysis starts. In this process, lipase hydrolyzes the triglycerides from the lipid substrate into a simpler form, such as free fatty acids and monoglycerides. Hence, the release of highly lipophilic drugs will be directly related with the lipolysis rate [17,19].

In blood, lipid droplets that possess apolipoprotein-CII at their surface undergo lipolysis, and the triglycerides of chylomicrons are hydrolyzed into free fatty acids by a protein anchored to the endothelium, called lipoprotein lipase (LPL). This lipolysis is an analogous process to that of duodenal lipolysis, with LPL, apolipoprotein-CII and albumin playing the role of pancreatic lipase, colipase and bile salts, respectively [20]. As in duodenal lipolysis, the release of highly lipophilic drugs will be directly related with the lipolysis rate [21,22].

Therefore, lipolysis is an interfacial process where the interfacial binding is a key rate-limiting step that controls the concentration of lipase at the interface, and hence the rate of lipolysis [23,24]. The interactions of interfacial structures with physiological media will determine the ultimate molecular composition and structure at the interface, and hence the extent of lipolysis both in digestive media and in the blood stream. Fundamental studies directed to the design of drug delivery systems need to be carefully designed in order to account for the more complex in vivo situation. In particular, it is important to evaluate the characteristics of block copolymers as emulsifiers as well as the interactions with physiological media. To accurately account for this double approach of the problem is the main goal of this review.

Significant advances have been made in the investigation of block copolymers. These advances have boosted the application of block copolymers from purely pharmaceutical issues to food products with specific functionalities. This review has two purposes. On one hand we overview current knowledge of the properties of block copolymers in bulk, interfaces and nanoemulsions. On the other hand, we look into the interactions of these systems with physiological media. The final objective is to correlate fundamental interfacial studies with the performance of block copolymers as nanocarriers for oral and parenteral administration. We will focus especially on recent experiments carried out at the University of Granada concerning interfacial properties and nanoemulsions of block copolymers. Hence, the work is divided in several sections. First we establish the main types of triblock copolymers studied in the literature and summarize their aggregation and self-assembly properties. The second section provides an overview of the current knowledge of the surface/interfacial properties of triblock copolymers. The third deals with nanoemulsions with copolymers as emulsifiers focusing on stability and rheology. The aim of the last section is to summarize and remark the relevance of the interfacial properties in the behavior of nanoemulsions to control their metabolic degradation within the human body. Poloxamers are promising emulsifiers able to protect the oil–water interface against the action of biological agents which are present during the lipolysis process, which is analogous under oral or intravenous conditions. Accordingly, understanding duodenal lipolysis onto the oil–water interface will provide generic information about interfacial mechanisms underlying not only lipolysis of nanoemulsions within the duodenum, but also through the intravenous route. We prove that addressing the interfacial behavior of block copolymers can provide basic information needed for the rational manipulation of food or pharmaceutical microstructures to control lipolysis as a crucial step to allow site-dependant controlled release of bioactive compounds.

2. Chemical structure of triblock copolymers

Triblock copolymers are macromolecules constructed by linking together three discrete linear chains (blocks) comprising chemically identical repeating units (monomers). These copolymers may be composed either of two similar blocks separated by a different block (ABA structure) or of three different blocks (ABC structure) [2]. The blocks may be hydrophilic, like poly(meth)acrylates, polypeptides, polysaccharides or polyurethanes, or of a hydrophobic nature, like poly(butylene oxide), poly(styrene oxide), polystyrene or polybutadiene, to name some examples [25–27]. In this review we will focus mainly on the