Available online at www.sciencedirect.com

ScienceDirect

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

Influence of hydroxypropyl methylcellulose, methylcellulose, gelatin, poloxamer 407 and poloxamer 188 on the formation and stability of soybean oil-in-water emulsions

Miao Zhang, Baixue Yang, Wei Liu, Sanming Li *

School of Pharmacy, Shenyang Pharmaceutical University, Benxi, Liaoning, China

ARTICLE INFO

Article history:
Received 19 February 2017
Received in revised form 3 May 2017
Accepted 20 May 2017
Available online

Keywords:
Polymers for pharmaceuticals
Emulsions
Physical stability
Stabilization mechanism

ABSTRACT

Macromolecules of polysaccharides, proteins and poloxamers have a hydrophobic portion and a hydrophilic one that can be used as emulsifiers. Parts of these emulsifiers are safe pharmaceutical excipients, which can replace the irritant low molecular weight surfactants to formulate emulsions for the pharmaceutical field. This project focused on preparing O/W emulsions stabilized with polymers for pharmaceuticals such as polysaccharides, proteins and poloxamers, including hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), gelatin, poloxamer 407 (F127) and poloxamer 188 (F68). Emulsion physical stability was assessed by centrifugation, autoclaving sterilization and droplet size measurements. The stabilization mechanisms of emulsions were determined by interfacial tension and rheological measurements. Results stated that the efficacy of these polymers for pharmaceuticals stabilized emulsions was sorted in the order: F127 > F68 > HPMC > MC > Gelatin.

1. Introduction

Emulsions are defined as a heterogeneous system consisting of two immiscible phases at least. Emulsifiers are added to the system to lower oil–water interfacial tension and improve the stability of emulsions by increasing repulsion forces between droplets [1,2]. The most common of pharmaceutical emulsifiers are low molecular weight surfactants, although they can cause toxic symptoms in organisms and produce serious environmental pollution [3]. In order to answer the increasing demand for clean label excipients, natural polymers can replace the potentially irritative low molecular weight surfactants used in pharmaceutical emulsions formulation [4]. Thus, developing much safer molecules for the preparation of emulsions would be a future trend. In natural polymers stabilized emulsions, polysaccharides and proteins generally act as biocompatible emulsifiers [5,6]. Polysaccharides display specific interfacial activity for their amphipathic structure that can be formed by two ways: (i) the protein moiety is linked covalently or physically to the polysaccharide, or (ii) the non-polar chemical groups are attached to the hydrophilic polysaccharide backbone [7,8]. Moreover, polysaccharides play an additional role as stabilizer to increase the viscosity of the continuous

* *Corresponding author*. School of Pharmacy, Shenyang Pharmaceutical University, Hongliu Road 85, Benxi, Liaoning 117004, China.
E-mail address: li_sanming@126.com (S. Li).

Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2017.05.009

phase that can slow the movement of the droplets, prevent phase separation and improve the long-term physical stability of emulsions [9]. Proteins contain hydrophilic and hydrophobic residues randomly spread all over the structure that are able to adsorb at the interface and facilitate droplets disruption by lowering the interfacial tension. The protein residues in the aqueous phase also provide steric stabilization against flocculation and coalescence [10]. Actually, polysaccharides and proteins are widely applied into food industry; however, pharmaceutical emulsions are mostly stabilized by low molecular weight surfactants [4,5,8]. It is worth mentioning that poloxamers as synthetic surfactants are widely used for pharmaceutical formulation [11]. Additionally, they are approved for oral or intravenous administration by the FDA by virtue of their high solubilizing capability, low toxicity and prolonged *in vivo* circulation time prior to dissociation [12]. However, poloxamers usually act as cosurfactants and combine with low molecular weight surfactants to prepare emulsions [13]. It is a fact that up to now, pharmaceutical emulsions have not evolved much compared to food emulsions. In the food industry, the better understanding of physicochemistry of natural polymers stabilized emulsions has been a successful approach for the formulation of highly stable emulsions [4]. Hence, systematic learning polymers acting as emulsifiers for pharmaceuticals is necessary.

In the present study, we chose polymers for pharmaceuticals to stabilize O/W emulsions: hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC), the major binder in tablets; gelatin, the main ingredient of hard capsules; and poloxamer 407 (F127) and poloxamer 188 (F68), the principal water-soluble base for many galenic applications (e.g., oral, rectal, topical, ophthalmic, nasal and injectable preparations) [4,14–16]. Indeed, these polymers also possess amphiphilic characteristic according to their structure.

HPMC and MC are water-soluble polysaccharides derived from cellulose, the most abundant polysaccharide in nature. Both HPMC and MC have the same polymeric backbone, a repeating structure of anhydroglucose units [17]. The units endow them the basic hydrophilic that can help themselves to adsorb onto the interface between two immiscible liquids [18]. Due to their hydrophilic character and high molecular weight, the viscosity of aqueous phase based on HPMC or MC system is high, decreasing the flowability and improving the rheological property [19]. HPMC and MC are thus good emulsifiers, enhancing droplet stability against flocculation and creaming [20,21].

Gelatin is a relatively high molecular weight protein obtained by partial hydrolysis of collagen and not by a single chemical substance [22]. The main constituents of gelatin are large and complex polypeptide molecules with the same amino acid composition, which confers interfacial activity to gelatin [23]. Also, it can lower the interfacial tension and adsorb at the oil–water interface preventing droplet from aggregating through the polymeric steric repulsion [22,24].

Poloxamers are block polymers that are synthesized by sequential addition of ethylene oxide (EO) and propylene oxide (PO) monomers in the presence of an alkaline catalyst, forming the basic A-B-A structure: EO_x-PO_y-EO_x [25]. F127 and F68 are produced by altering the number of hydrophilic $EO_{(x)}$ and hydrophobic $PO_{(y)}$ units [26]. This structure confers an amphiphilic character to the copolymers and allows them strong adsorption at oil–water interfaces to form stabilizing layers around oil droplets, so they are able to fulfill both the emulsifying and the stabilizing roles [27].

The purpose of this study was to exclusively use HPMC, MC, gelatin, F127 and F68 to prepare stable O/W emulsions, evaluate the physical stability of these emulsions, investigate their stabilization mechanisms and compare the interfacial activity of these emulsifiers. The assessment of emulsion stability was conducted over a 3-month period, combining different methods such as centrifugation, autoclaving sterilization and droplet size measurements. Moreover, the stabilization mechanisms of emulsions were analyzed by interfacial tension and rheology measurements, which favored to get better insight into the stable emulsions and choose the better emulsifiers among these polymers for pharmaceuticals.

2. Materials and methods

2.1. Materials

HPMC (K100M) was a kind gift from Shanghai Colorcon Coating Technology Limited (Shanghai, China). MC (with an average molecular weight of about 20,000 g/mol as reported by the supplier) and Gelatin (Type A gelatin, pI ~ 7–9) was purchased from Tianjin Bodi Chemical Co., Ltd. (Tianjin, China). F127 (with an average molecular weight of about 12,962 g/mol as reported by the supplier) and F68 (with an average molecular weight of about 8622 g/mol as reported by the supplier) were supplied by BASF Company Ltd. (Shanghai, China). Injectable soybean oil was purchased from Zhonghang Tieling Pharmaceutical Co., Ltd. (Tieling, China). Experiments were carried out with deionized water.

2.2. Methods

2.2.1. The preparation of emulsions

O/W emulsions were prepared by the following steps. Firstly, different mass fractions of emulsifiers and a certain amount of oil were well mixed in a mortar. Deionized water was added to the mortar with constant grinding to prepare mixture. In this system, oil:aqueous phase ratio was 15:85 by weight. Then, the mixture underwent ultrasonic processing by Ultrasonic Cell Crusher (JY92-IIN, Ningbo Xinzhi Biological Co., Ltd., China) for 2 min; this was repeated five times to prepare coarse emulsions. At last, the final emulsions were obtained after high pressure homogenization (Niro Soavi NS10012K homogenization, Via M. da Erba Edoari, Italy) at 700 bar for three, five, eight and fifteen times circulation, respectively. Before homogenization, the pH of the coarse emulsions was adjusted to 8.0 with 0.1 mol/L NaOH.

2.2.2. Droplet size

Creaming would be formed after an increase in droplet size of emulsions [5]. Therefore, it is a convenient way to evaluate emulsion physical stability by determining and comparing droplet size in different time intervals to observe the minimal changes of emulsion droplets.

A dynamic light scattering (Zetasizer Nano-ZS90, Malvern, UK) was used for the droplet size measurement of emulsions, whose characteristic size was always included in the instrument

Please cite this article in press as: Miao Zhang, Baixue Yang, Wei Liu, Sanming Li, Influence of hydroxypropyl methylcellulose, methylcellulose, gelatin, poloxamer 407 and poloxamer 188 on the formation and stability of soybean oil-in-water emulsions, Asian Journal of Pharmaceutical Sciences (2017), doi: 10.1016/j.ajps.2017.05.009