International Journal of Pharmaceutics xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen

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ARTICLE INFO

Article history:
Received 15 January 2017
Received in revised form 7 April 2017
Accepted 9 April 2017
Available online xxx

Keywords:
Nanostructured Lipid Carriers (NLC)
Hydrogels
Mucoadhesion
Buccal mucosa

ABSTRACT

The lipid nanoparticles, namely Nanostructured Lipid Carriers (NLC), as drug delivery systems have been investigated for several years.

One of the delivery routes for which these carriers can be applied is buccal administration. However, the liquid dispersions of lipid nanoparticles can be rapidly removed from oral cavity by saliva. Thus, the development of a system that allows increased retention time on the mucosa is necessary. For this reason, the development of mucoadhesive preparations for buccal administration of lipid nanoparticles becomes important.

Hydrogels prepared with mucoadhesive polymers (Carbopol® 980 and polycarbophil) constitute a promising option. The aim of this work was to develop mucoadhesive buccal hydrogels with NLC, using ibuprofen as a model drug.

The obtained results showed that the developed NLC dispersions presented particles in the nanometric size range, with low polydispersity index values and efficient ability for the entrapment of the model drug. Moreover, the incorporation of NLC in hydrogels of mucoadhesive polymers resulted in preparations with desirable rheological features as well as texture (firmness and adhesiveness) and mucoadhesive properties, which could benefit the therapeutic efficacy, by increasing the residence time and easiness for topical application in the buccal mucosa. Additionally, the developed preparations exhibited sustained drug release as intended for these systems.

1. Introduction

During the last years, lipid nanoparticles have remained the first choice in the development of new drug delivery systems, as they present the advantages of the traditional colloidal systems, and avoid some of their problems: (i) use of lipids and surfactants generally recognized as safe (GRAS), which predicts excellent tolerability for humans; (ii) protection of encapsulated drugs and a reduction on their mobility, allowing a controlled release; (iii) improvement of physical stability and drug biocompatibility; (iv) possibility of specific drug targeting; (v) easiness of up-scaling of the production methods (Müller et al., 2000; Müller et al., 2002).

Lipid nanoparticles can be distinguished in two main types, namely, Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC). In the first generation, the so-called SLN, nanoparticles consist in a solid lipid matrix, obtained only from solid lipids, that is stabilized by a layer of one or more surfactants. In contrast, NLC, the second generation, are composed by a blend of a solid lipid with a liquid lipid. However, the lipid matrix remains solid at room and body temperature. The NLC systems appear to overcome some of the shortcomings of the SLN systems, such as insufficient drug loading capacity and poor long-term stability related with drug expulsion during storage (Mehnert and Mäder, 2001; Müller et al., 2002).

There are two main production techniques to obtain lipid nanoparticles, high pressure homogenization (HPH) and high speed homogenization followed by sonication (HSH). HPH technology has emerged as an established and potent technique for production of lipid nanoparticles. One of its main advantages include easiness to scale-up, since this technology is already applied in pharmaceutical industry, in the production of nano-emulsions for parenteral nutrition (Schuh et al., 2014). HSH presents as a major disadvantage, the fact that it does not produce narrow particle size distributions. However, unlike HPH, HSH

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http://dx.doi.org/10.1016/j.ijpharm.2017.04.025
0378-5173/

requires simple instruments that can be found in every laboratory (Naseri et al., 2015).

One of the delivery routes for which lipid nanoparticles can be applied is buccal administration. Oral mucosa offers several advantages for drug delivery, such as high vascularization, promoting a systemic effect; the avoidance of first-pass metabolism; relatively low enzymatic activity, which could improve drug bioavailability; and, therefore, patient compliance (Silva et al., 2012b). Furthermore, drug administration to specific sites in the oral cavity constitute the common treatment of bacterial and fungal infections, toothaches, periodontal disease and others (Shojaei, 1998).

Besides the advantages of lipid nanoparticles as drug delivery systems, liquid dispersions of lipid nanoparticles can be rapidly removed from oral cavity through saliva action, which can lead to a rapid elimination of drugs by involuntary swallowing and consequently may require various administrations (Bhati and Nagrajan, 2012; Sohi et al., 2010). Additionally, since lipid nanoparticles promote a sustained drug release, its buccal administration with a view to a systemic effect only makes sense if the retention on the mucosa is prolonged. For this reason, the development of mucoadhesive preparations for buccal administration of lipid nanoparticles is important. Hydrogels obtained with mucoadhesive polymers constitute a promising option, since it allows close contact with the buccal mucosa, providing adhesiveness and prolonging the residence time of the dosage form (Hamidi et al., 2008; Shaikh et al., 2011). These systems may be obtained with polyacrylic acid derivatives, such as the case of Carbopol® 980 and polycarbophil (Liu et al., 2008; Zhu et al., 2013). Although the exact mechanism is not well understood, it is believed that polyacrylic acid polymers interact with mucin, resulting in adhesion of the polymer to mucin (Lubrizol, 2011; Smart, 2005; Zhu et al., 2013).

The aim of this work was to develop and characterize NLC dispersions containing ibuprofen, used as a model drug, in addition to the development and technological characterization of mucoadhesive buccal hydrogels with Carbopol® 980 and polycarbophil incorporating the obtained lipid nanoparticles.

2. Materials and methods

2.1. Materials

Miglyol® 812, ibuprofen, glycerol, triethanolamine and Tween® 80 were purchased from Acofarma (Spain). Cetrimide was purchased from José M. Vaz Pereira (Portugal). Precirol® ATO 5 was supplied by Gattefossé (France). Polyacrylic acid derivatives [Carbopol® 980 and polycarbophil (Noveon® AA-1)] were kindly supplied by Lubrizol® (USA). Sodium chloride was obtained from VWR International (Portugal), dibasic phosphate from Sigma-Aldrich (Portugal), monopotassium phosphate and phosphoric acid from PanReac (Spain), being these reagents used to prepare the pH 7.4 buffer solution and the simulated saliva solution.

2.2. Preparation of NLC dispersions

Firstly, lipids were heated 5–10 °C above the solid lipid (Precirol® ATO 5) melting point (55.2 °C). At the same time, the aqueous phase was prepared by dissolving the surfactant (Tween® 80) and the preservative (cetrimide) in purified water and heated at the same temperature of the lipid phase. After the melting of the lipid phase, the aqueous phase was added to the former and homogenized under high-speed stirring, using an Ultra-Turrax® T25 (IKA, Germany), at 13,500 rpm for 3 min. Dispersions of NLC were obtained through this pre-emulsion by two different methods: (a) using a sonication probe (Ultrasonic processor Vibra cell®, Sonic & Materials, Newtown, USA) at 70% of amplitude for 10 min (HSH); or (b) using a high pressure homogenizer (Stansted Fluid Power, UK), performing 3 cycles of 500 bar (HPH). The obtained O/W nanoemulsions were immediately transferred to glass vials and cooled down to room temperature to originate the solid nanoparticles dispersed in the aqueous phase. For each method (HSH and HPH), a placebo dispersion (without ibuprofen) and a dispersion of NLC incorporating the model drug at a concentration of 0.25% (w/w) were obtained. When applicable, ibuprofen was dissolved in the lipid phase.

Table 1 presents the composition of obtained dispersions.

2.3. Characterization of NLC

2.3.1. Particle size, polydispersity index and zeta potential

The mean particle size, polydispersity index (PI) and zeta potential (ZP) were determined by dynamic light scattering (DLS) and electrophoretic mobility, respectively, using a particle size and ZP analyzer (Brookhaven Instruments, Holtsville, NY, USA).

DLS measures the fluctuation on the intensity of the scattered light caused by particle movement and represents one of the most powerful techniques to assess particle size (Finsy and De Jaeger, 1991). Before measurement, NLC dispersions were diluted with purified water in order to avoid the multi-dispersion of the light caused by a high concentration of particles (Mendes et al., 2013).

All experiments were performed at 25 °C, on the day NLC were prepared. Results of particle size, PI and ZP were presented as the mean value ± standard deviation (SD) of six runs.

2.4. Determination of drug entrapment efficiency

2.4.1. Spectrophotometric method

The quantification of ibuprofen was performed by UV/Vis spectrophotometry method, partially validated for linearity, repeatability and specificity, accordingly to International Conference on Harmonization (ICH) guideline for validation of analytical methods (International Conference on Harmonization, 2005), at 222 nm using a V-650 UV/Vis Spectrophotometer (Jasco, Japan). A calibration curve of different ibuprofen concentrations (0, 0.002, 0,004, 0.008, 0.01, 0.012 mg/ml) versus absorbance was plotted and the linear equation $y = 48.959\ x + 0.025$ was obtained with a correlation coefficient of 0.994.

2.4.2. Entrapment efficiency and loading capacity

The entrapment efficiency (EE) and loading capacity (LC) were indirectly determined, calculating the amount of free ibuprofen in the aqueous phase, applying Eqs. (1) and (2), respectively (Souto and Muller, 2010):

$$EE\ (\%) = ((\text{Total amount of ibuprofen} - \text{Amount of free ibuprofen})/\text{Total amount of ibuprofen}) \times 100 \quad (1)$$

Table 1
Composition of placebo and ibuprofen-loaded NLC dispersions produced by sonication (NLC_{PS} and NLC_{IS}, respectively) and by HPH (NLC_{PP} and NLC_{IP}, respectively).

Composition		Formulation (%, w/w)			
		NLC_{PS}	NLC_{IS}	NLC_{PP}	NLC_{IP}
Lipid phase	Precirol® ATO 5	7.0	7.0	7.0	7.0
	Miglyol® 812	3.0	3.0	3.0	3.0
	Ibuprofen	–	0.25	–	0.25
Aqueous phase	Tween® 80	2.5	2.5	2.5	2.5
	Cetrimide	0.1	0.1	0.1	0.1
	Purified Water	q.s.100	q.s.100	q.s.100	q.s.100

Please cite this article in press as: A.C. Marques, et al., Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen, Int J Pharmaceut (2017), http://dx.doi.org/10.1016/j.ijpharm.2017.04.025