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Original Research Article

Enhanced anti-inflammatory benefits of meloxicam-loaded lipid-core nanocapsules in a mouse pleurisy model: A comparative study with a free form drug

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ABSTRACT

The development of new treatments for inflammation continues to be of high interest, since long-acting effect is critical for patients. We investigated whether meloxicam-loaded lipid-core nanocapsules (M-NC) have an anti-inflammatory action superior to a free drug (M-F) on a mouse pleurisy model, by analyzing the time-course of leukocytes migration in the pleural fluid. Male adult Swiss mice were divided into six groups for each time (24; 48 and 72 h) and were pretreated with blank nanocapsules (17 ml/kg) or M-NC (5 mg/kg) or free meloxicam (M-F) (5 mg/kg). After pretreatments, mice received saline (0.9%) or carrageenan (Cg) (1%) into pleural cavity. Four hours after Cg or saline administration, animals were killed, pleural cavity was washed and pleural fluid was collected for the determination of total leukocytes. Cytokines levels, differential leukocyte count and α-1-acid glycoprotein (AGP) levels were determined only at 48 h of pretreatment, which had effect on total leukocyte count. M-NC were effective against the increase in total and differential leukocyte counts and pleural exudate caused by Cg, while M-F had no effect. M-NC had superior

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Abbreviations:
M-NC, meloxicam-loaded lipid-core nanocapsules
M-F, free meloxicam

effect to M-F against the increase in cytokines and AGP levels induced by Cg. In summary, M-NC had a superior anti-inflammatory effect to free drug in Cg-induced pleurisy, supporting the idea that the inflammatory process in tissues facilitates the vectorization of polymeric nanoparticles.

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Introduction

Nanotechnology offers broad applications in different areas: environmental bioprocessing, food industry, improvement of agricultural systems and healthcare (Bogunia-Kubik and Sugisaka, 2002). Moreover, when healthcare is taken into consideration, nanotechnology is applied for medicines, bioimaging, diagnostics, tissue engineering and treatments (Moghimi et al., 2005; Berger, 2011). In fact, nanomedicine brings together chemists, physicists, and biologists in a more interdependent manner than conventional drug development, being wide ranging in concept and design (Berger, 2011; Brown and Patel, 2015).

Polymeric nanoparticles are systems of great interest for nanomedicine, since they modify drug delivery technology (Kulhari et al., 2014). In fact, nanocapsules can be defined as nanovesicles in which the drug is present in the oily core or polymer wall (Anton et al., 2008). Polymeric nanoparticles have been developed for the purpose of directing and controlling the gradual release of drugs in action site (Sakata et al., 2007), increasing the bioavailability in targeted area, as well as reducing side effects (Lee et al., 2012; Kulhari et al., 2014). An important property of nanocapsules is to minimize the side effects by reducing the irritation at administration site and protecting the drug degradation during storage and after administration (Couvreur et al., 2002). In this way, nanotechnology has been used to improve the pharmacological effects of various drugs in different experimental models (Bender et al., 2012; Ianiski et al., 2012; Badran et al., 2014; Villalba et al., 2014).

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class widely used to control the inflammatory process; however, they have side effects that make the limited treatment. Meloxicam is a NSAID that selectively inhibits the cyclooxygenase-2 (COX-2) activity (Pairet et al., 1998), and thus prostaglandin synthesis (Gupta et al., 2002). This drug has less adverse effects than other NSAIDs (Pairet et al., 1998; Van-Antwerpen and Neve, 2004; Arafa et al., 2007), but it has a high rate of plasma protein binding and low apparent distribution volumes, which decreases its pharmacological effect (Seedher and Bhatia, 2005). In this context, nanotechnology has been carried to correct this problem.

Previous studies of our research group demonstrated that meloxicam-loaded lipid-core nanocapsules (M-NC) had superior pharmacological effect to free drug in several models, such as antinociceptive and antiedematogenic effects in acute models of nociception (Villalba et al., 2014) and protective effect against amyloid-β peptide-induced damage (Ianiski et al., 2012). However, the anti-inflammatory effect of M-NC was not studied until this moment.

In view of the above considerations, the aim of the present study was to investigate whether M-NC have an superior anti-inflammatory action to free drug on a mouse pleurisy model, by analyzing the time-course of leukocytes migration in the pleural fluid. The anti-inflammatory action of M-NC was also investigated by evaluating the pleural exudate accumulation, pro-inflammatory cytokines and α-1-acid glycoprotein (AGP) levels in the pleural fluid.

Materials and methods

Drugs

Carrageenan (Cg) was purchased from Sigma (St. Louis, MO, USA). All other chemicals were obtained from standard commercial suppliers.

Lipid-core nanocapsules

M-NC suspensions were prepared by interfacial deposition of preformed polymer (adapted from Fessi et al., 1989) at a concentration of 0.3 mg/ml. Aqueous phase was composed of water (530 ml) and polysorbate 80 (0.766 g). Organic phase was composed by meloxicam (0.03 g), poly-ε-caprolactone (1.0 g), sorbitan monostearate (0.766 g), caprylic/capric triglyceride (3.1 g) and acetone (270 ml). Organic phase was added under magnetic stirring into aqueous phase. Suspensions of blank nanocapsules (B-NC) were prepared using the same protocol of M-NC, but without the presence of drug.

The particle size, polydispersity index and zeta potential of M-NC and B-NC were measured by photon correlation spectroscopy. Samples were diluted in Milli-Q water (1:500) and analysis was performed at 25 °C, using a Zetasizer® (Nanoseries, Malvern, UK). The pH values of suspensions were determined using a potentiometer Denver® (Ultrabasic). The amount of meloxicam in nanostructures was determined by high performance liquid chromatography (HPLC). Each sample was analyzed in triplicate.

Physical-chemical analyses of suspensions demonstrated that particle diameter was 247 ± 9 nm and 212 ± 10 nm for M-NC and B-NC, respectively. Moreover, polydispersity index was 0.14 ± 0.02 nm and 0.10 ± 0.01 nm for M-NC and B-NC, respectively. Zeta-potential was −36.4 ± 4.4 mV for M-NC and −35.0 ± 2.5 mV for B-NC, and pH values were 5.5 ± 0.2 and 6.1 ± 0.2, respectively. Meloxicam content in nanocapsules after preparation was close to theoretical value, indicating that there was no degradation of the drug during the preparation of suspensions. Encapsulation efficiency was around 98%.

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