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Research paper

Carvedilol-loaded nanocapsules: Mucoadhesive properties and permeability across the sublingual mucosa

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ABSTRACT

Carvedilol is a drug used to treat heart failure, hypertension, and coronary artery diseases . However, it has low oral bioavailability (25–35%) due to its high first-pass hepatic metabolism. The objective of this study was to develop carvedilol-loaded mucoadhesive nanocapsules as delivery systems for the sublingual administration of the drug. Nanocapsules were prepared using poly(ε-caprolactone) (CAR-LNC) and Eudragit® RS 100 (CAR-NC) as polymeric wall. *In vitro* interaction of formulations with mucin was performed to predict their mucoadhesion capacity. The permeability and washability profiles of carvedilol were evaluated using porcine sublingual mucosa. The mean diameter of particles in formulations was in the nanometric range, and particles had low polydispersity and slightly acidic pH. Zeta potential values were positive for CAR-NC and negative for CAR-LNC. Encapsulation efficiency was higher than 87% and 99% for CAR-NC and CAR-LNC, respectively. Both formulations presented controlled drug release profiles and mucoadhesive properties. Carvedilol was able to permeate through the sublingual mucosa. Nanoencapsulation improved retention time on the mucosa and permeation in presence of simulated salivary flux. This study highlighted the suitability of using CAR-loaded nanocapsules in the development of innovative sublingual dosage forms.

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1. Introduction

Carvedilol (CAR) has been used for the management of important cardiovascular diseases, which are the main causes of worldwide morbidity and mortality. According to the World Health Organization (WHO), in 2012 17.5 million people died from cardiovascular diseases, and according to WHO it has also been estimated that more than 22.2 million people will die of these conditions in the year 2030 [1]. CAR is a non-selective β-adrenoceptor antagonist, α1-adrenoceptor blocker, and has antioxidant effects. It has been approved for the treatment of heart failure, hypertension, and coronary artery diseases [2]. This drug is available as tablets for oral administration; however, its systemic bioavailability is only 25–35% due to extensive hepatic first-pass metabolism [3]. In order to increase bioavailability, different strategies have been proposed for oral and nasal administration of CAR [4–6]. The sublingual route of administration is a motivating alternative when the aim is to improve the bioavailability of drugs that undergo first-pass metabolism. Since this region is highly vascularized, the drug can enter the systemic circulation directly, bypassing hepatic metabolism. However, this cavity is exposed to constant flow of saliva, and part of the drug may therefore be swallowed [7]. In order to prolong retention time in this area, studies have suggested the use of mucoadhesive systems, which are able to interact with the mucus layer covering the surface of buccal epithelia [8,9].

Nanoparticles are promising drug carriers that have been extensively studied. These structures can control drug release, enhancing the desired effect by lowering the number of daily administrations, in addition to the possibility to reduce doses and mitigate side effects [10]. Polymeric nanocapsules are structures in which the drug is confined in an oily core surrounded by a polymeric wall [11]. The development of nanocapsules using polymers with mucoadhesive properties points to the potential of these structures as drug carriers to be administered through the sublingual route. Both poly(ε-caprolactone) (PCL) and Eudragit® RS100 (EUD), a co-polymer of poly(ethylacrylate, methyl–methacrylate methacrylic acid ester), present interesting bioadhesive properties [9,12]. These two polymers have been used

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to prepare nanocapsules for different purposes, from cutaneous administration to brain delivery [11,13–16].

In view of the considerable influence of cardiovascular disease on worldwide morbidity and mortality and the multiple cardiovascular action of CAR, the design of pharmaceutical formulations to improve bioavailability of this drug becomes an important subject in research. In this scenario, this study describes a nanoencapsulation process for CAR in polymeric nanocapsules with mucoadhesive properties, to improve the drug's sublingual retention and permeability. To the best of our knowledge, this is the first report on the development of polymeric nanocapsules intended to sublingual administration.

2. Methods

2.1. Materials

Carvedilol was obtained from Henrifarma (São Paulo, Brazil). Poly(ε-caprolactone) (MW 80,000), sorbitan monostearate and mucin from porcine stomach (type II) were acquired from Sigma-Aldrich (São Paulo, Brazil). Eudragit® RS100 was supplied by Degussa (Darmstadt, Germany), and grape seed oil was obtained from Dellaware (Porto Alegre, Brazil). Polysorbate 80, acetone, and hydrochloric acid were purchased from Vetec (Rio de Janeiro, Brazil). Basic fuchsine, sodium metabisulphite, periodic acid, and acetic acid were supplied by Dinamica (São Paulo, Brazil). Potassium phosphate was purchased from Nuclear (São Paulo, Brazil), while sodium hydroxide was bought from Cromoline (São Paulo, Brazil). HPLC grade acetonitrile was purchased from Tedia (Rio de Janeiro, Brazil).

2.2. Preparation of nanocapsule suspensions

Nanocapsules were developed by interfacial deposition of preformed polymer [17,18]. For the preparation of EUD nanocapsules (CAR-NC), an organic phase was formulated dissolving 0.1 g of polymer (EUD), 165 μL of grape seed oil, and 5 mg of CAR (0.5 mg mL^{-1}) in 27 mL of acetone with magnetic stirring at 40 °C. To obtain PCL lipid-core nanocapsules (CAR-LNC), the organic phase was prepared in the same way, but replacing EUD by PCL and adding 0.0385 g of sorbitan monostearate [18]. The organic phase was injected into 53 mL of an aqueous phase containing 0.077 g of polysorbate 80 with magnetic stirring at 40 °C. After, acetone was removed and the suspension was concentrated under reduced pressure (Rotavapor R-114, Buchi, Flawil, Switzerland) to the final volume of 10 mL. Formulations without drug were also prepared (NC or LNC).

2.3. Analytical method

The CAR assay was carried out by high performance liquid chromatography (HPLC), using a method adapted from Ieggli et al. (2011) [19] and validated considering the purposes of this study. Analyses were performed in a Shimadzu LC system (Kyoto, Japan) equipped with a CBM-20A system controller, a LC-20AT pump, a DGU-20A5 degasser, a SIL-20A auto-sampler, and a SPD-20AV detector (UV). A Phenomenex Luna C_{18} column (250 mm × 4.6 mm I.D., with a particle size of 5 μm) was utilized as stationary phase. The mobile phase was composed of phosphoric acid pH 3.0/acetonitrile (50:50, v/v), run at a flow rate of 0.8 mL min^{-1}. UV detection was carried out at 241 nm, and run time was 10 min. For drug content and encapsulation efficiency analysis, an injection volume of 10 μL was used. For *in vitro* drug release, permeability and washability studies, the injection volume was changed to 20 μL in order to lower the quantification limit. Furthermore, the mobile phase was changed to phosphoric acid pH 3.0/acetonitrile (60:40, v/v) for the permeability and washability studies in order to improve resolution between chromatographic peaks. Specificity, linearity, intraday (n = 6) and interday (n = 9) precision were evaluated for all methods according to the official guidelines [20].

2.4. Physicochemical characterization

Volume-weighted mean diameters ($D_{4,3}$) and polydispersity (Span) (n = 3) were analyzed by laser diffraction (LD) (Mastersizer 2000, Malvern Instruments Ltd., UK). The sample was dropped directly into the disperser compartment of equipment containing 150 mL of water until the adequate obscuration index (2–8%) was reached. Mean particle size and polydispersity index (IPD) (n = 3) were measured using dynamic light scattering (DLS) (ZetaSizer Nano ZS, Malvern Instruments Ltd., UK) after dilution of the suspensions (20 μL) in water (10 mL) previously filtered (0.45 μm, Millipore®). Zeta potential was determined (n = 3) by electrophoretic mobility (ZetaSizer Nano ZS, Malvern Instruments Ltd., UK). Samples (20 μL) were diluted in NaCl solution 10 mM (10 mL) previously filtered (0.45 μm, Millipore®). pH (n = 3) was measured with a potentiometer (VB-10, Denver Instrument, USA) using the original, undiluted formulations directly. The morphology was analyzed by transmission electron microscopy (TEM, Jeol JEM 1200-ExII, 100 mV, Tokyo, Japan) at the Microscopy Center of the University (Centro de Microscopia Eletrônica - UFRGS, Brazil). Samples were diluted (1:10 v/v) in ultrapure water, placed on a specimen grid (Formvar-Carbon support film, Electron Microscopy Sciences, USA), and negatively stained with uranyl acetate solution (2%, w/v).

2.5. Drug content and encapsulation efficiency

CAR was assayed (n = 3) by HPLC according to the method previously described, after dissolution of suspensions (1.0 mL) in acetonitrile (9.0 mL) followed by sonication (10 min). This dispersion was centrifuged at 4120*g* for 10 min. After, an aliquot (2.0 mL) of the supernatant was diluted to 10 mL in mobile phase and analyzed. Encapsulation efficiency was calculated (n = 3) based on the difference between total drug and free drug contents in the ultrafiltrate, obtained by ultrafiltration/centrifugation (Ultrafree-MC 10,000 MW, Millipore, Billerica, USA) at 4120*g* for 10 min. In order to detect any interaction between the drug and the membrane, this experiment was also carried out using a solution of CAR, under the same conditions, and drug recovery was determined in the ultrafiltrate. The method had specificity, good linearity (r = 0.999, n = 3) in the range of 1.00–20.00 μg·mL^{-1}, and suitable intra- (SD = 1.25%) and interday (SD = 1.02%) precision. Limit of detection (LoD) and limit of quantification (LoQ) were 0.296 and 0.896 μg·mL^{-1}.

2.6. In vitro drug release

The *in vitro* release of CAR (n = 3) from nanocapsules and from a hydroalcoholic (ethanol: water 50:50 v/v, 0.50 mg mL^{-1}) solution (CAR-S) was carried out using the dialysis bag method. Formulations (2 mL) were placed in a dialysis tubing cellulose membrane (flat width of 25 mm, molecular weight cut-off 14,000, Sigma-Aldrich, São Paulo, Brazil) and suspended in 100 mL of release medium (sodium phosphate buffer pH 6.8, 0.2 M). The samples were maintained in a bath at 37 °C with agitation of 70 ± 10 rpm. At predetermined time intervals, external medium (1.0 mL) was withdrawn and directly analyzed by HPLC (Section 2.5). Sink condition was maintained during the whole experiment. The solubility of the drug in the medium was around 60 μg·mL^{-1}, at least 6× higher than the expected total drug concentration after 100% of

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