Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 291 (2005) 69–77
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Development and bioadhesive properties of chitosan-ethylcellulose microspheres for nasal delivery

A. Martinac[a], J. Filipović-Grčić[a,*], D. Voinovich[b], B. Perissutti[b], E. Franceschinis[b]

[a] *Department of Pharmaceutics, Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, Zagreb, Croatia*
[b] *Department of Pharmaceutical Sciences, University of Trieste, P. le Europa 1, Trieste, Italy*

Received 27 January 2004; received in revised form 18 June 2004; accepted 19 July 2004
Available online 31 December 2004

Abstract

Loratadine-loaded microspheres were prepared by spray-drying of dispersions, emulsions and suspensions differing in polymeric composition and solvents used. Conventional microspheres were obtained by spray-drying of dispersions composed of chitosan (CM) as only polymer, while composed microspheres were obtained by spray-drying of two-phase systems composed of chitosan and ethylcellulose (EC). Microspheres differed in EC/CM weight ratio (0:1, 1:2 and 1:3) and in loratadine/polymers weight ratio (1:6 and 1:8).

The entrapment efficiencies were between 67.9 and 86.1%; less loratadine was entrapped as polymer/drug ratio decreased. In comparison to one-phase systems composed of CM as only polymer, spray-drying of two-phase systems composed of both, CM and EC resulted in improved loratadine entrapment (80.1–86.1%). All microspheres were positively charged, indicating the presence of chitosan at the surface, regardless of the drug content and the type of spray-dried system. The highest zeta-potential was measured for loratadine-free conventional microspheres, consisting of chitosan only (32.7 ± 1.3 mV). Tensile studies showed that both, EC/CM ratio and the type of spray-dried system influenced the bioadhesive properties of the microspheres in a way that the microspheres with higher chitosan content were more bioadhesive and microspheres prepared from suspensions were more bioadhesive than those prepared from emulsions, regardless of the same polymeric composition. The results suggested that the spray-drying method is useful to produce bioadhesive loratadine-loaded microspheres.

Keywords: Chitosan; Ethylcellulose; Microspheres; Nasal delivery; Bioadhesion; Drug delivery systems

1. Introduction

Microspheres, in general, are investigated for targeted and controlled release drug delivery. A polymeric device allows for slow, controlled, and predictable drug release over a period of time and hence reduces the overall amount of drug needed (Illum, 2003). In nasal

* Corresponding author. Tel.: +385 1 46 12 608; fax: +385 1 46 12 691.
E-mail address: jelena.filipovic-grcic@fbf.htnet.hr (J. Filipović-Grčić).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.07.044

drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa (Vasir et al., 2003).

The aim of this work was to develop bioadhesive microspheres for nasal delivery of lipophilic model drug loratadine. Loratadine is a second-generation antihistamine that is rapidly absorbed after oral administration and reaches peak plasma levels within 1–2 h. It undergoes extensive first-pass metabolism in the liver. Topical antihistamines are as effective as oral and may be more beneficial in relieving nasal obstruction. Although there is little difference with regard to speed of onset of clinical activity, unvanted effects are reduced and the preparations can be prescribed without risk of interactions with any concomitant medications (Trigg and Davies, 1996). Polymers used for the microsphere preparation were chitosan (CM) and ethylcellulose (EC).

Chitosan is a biocompatible and biodegradable polycationic polymer with low toxicity. The positive charges on the chitosan polymer can give rise to a strong electrostatic interaction with mucus or a negatively charged mucosal surface. This is to provide a longer contact time for drug transport across the nasal membrane, before the formulation is cleared by the mucociliary clearance mechanism (Singla and Chawla, 2001). Thus, investigation of the zeta-potential is an important part of the microsphere characterization, as the zeta-potential has a substantial influence on the adhesion of drug delivery systems onto biological surfaces (Berthold et al., 1996).

Microspheres were produced by spray-drying. The drug encapsulation efficiency, the size and morphology, the zeta-potential and bioadhesive properties were studied as a function of type of spray-dried system, polymeric composition and the drug content.

2. Materials and methods

2.1. Reagents and chemicals

The following materials were used as received: Chitosan of medium molecular weight, CM (M_r 400 000; deacetylation degree 83.5%, Fluka, Buchs, Switzerland), ethylcellulose, EC (Sigma, St. Louis, USA), loratadine (Pliva d.d., Zagreb, Croatia). Buffer substances and all other chemicals or solvents used were of analytical grade and purchased from Kemika (Croatia).

2.2. Preparation of microspheres

Drug-free and drug-loaded microspheres based on chitosan were prepared by spray-drying of simple dispersion, oil-in-water (O/W) emulsion and suspension, using a Büchi 190 mini spray drier (Flawil, Switzerland) with a standard 0.5 mm nozzle. The liquid was fed to the nozzle with peristaltic pump, atomised by the force of the compressed air and blown together with a hot air to the chamber where the solvent in the droplets was evaporated. The dry product was then collected in a collection bottle. The drying conditions were as follows: spray flow rate of 0.25 l h^{-1}, compressed air flow rate of 700 Nl h^{-1}, inlet air temperature of 135 °C and outlet air temperature of 85 °C.

For the simple dispersion system chitosan was solubilized in 0.5% acetic acid solution at 1% (w/v) concentration. Loratadine was dissolved at two different concentrations (1 and 0.75%, w/v) in 96% ethanol. These solutions were than mixed with chitosan solution in a 1:6 (v/v) ratio and subjected to spray-drying under process conditions described above. In that way, two different polymer/drug ratios (6:1 and 8:1, w/w) were obtained for the preparation of loratadine-loaded chitosan microspheres.

For the O/W emulsion system, the oil phase consisted of EC dissolved in ethyl acetate (4%, w/v), and chitosan solution (1%, w/v) in 0.5% (v/v) acetic acid represented water phase. Loratadine was dissolved in oil phase at the concentration of 2% (w/v), resulting in loratadine/EC ratio of 1:2 (w/w).

Emulsions were prepared by ultrasonic homogenisation (Cole-Parmer 4710 Series, USA; 2×30 s, at 60 μW, with 30 s intervals) of the oil phase and the part of the water phase, and were later diluted with the rest of the water phase. O/W emulsions prepared differed in volume oil/water phase ratios that were 1:8 and 1:12. Theoretical polymer/drug ratios were 6:1 and 8:1 (w/w), respectively.

Emulsions were stirred for 10 or 120 min using magnetic stirrer (900 rpm) and were then subjected to spray-