Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 288 (2005) 295–303
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Mucoadhesive microspheres prepared by interpolymer complexation and solvent diffusion method

Myung-Kwan Chun[a], Chong-Su Cho[b], Hoo-Kyun Choi[a,c,*]

[a] *College of Pharmacy, Chosun University, 375 Seoseok-dong, Dong-gu, Gwangju 501-759, Republic of Korea*
[b] *School of Agricultural Biotechnology, Seoul National University, Seoul, Republic of Korea*
[c] *Research Center for Resistant Cells, Chosun University, Republic of Korea*

Received 15 July 2004; received in revised form 4 October 2004; accepted 15 October 2004

Abstract

Mucoadhesive microspheres were prepared to increase gastric residence time using an interpolymer complexation of poly(acrylic acid) (PAA) with poly(vinyl pyrrolidone) (PVP) and a solvent diffusion method. The complexation between poly(acrylic acid) and poly(vinyl pyrrolidone) as a result of hydrogen bonding was confirmed by the shift in the carbonyl absorption bands of poly(acrylic acid) using FT-IR. A mixture of ethanol/water was used as the internal phase, corn oil was used as the external phase of emulsion, and span 80 was used as the surfactant. Spherical microspheres were prepared and the inside of the microspheres was completely filled. The optimum solvent ratio of the internal phase (ethanol/water) was 8/2 and 7/3, and the particle size increased as the content of water was increased. The mean particle size increased with the increase in polymer concentration. The adhesive force of microspheres was equivalent to that of Carbopol. The release rate of acetaminophen from the complex microspheres was slower than the PVP microspheres at pH 2.0 and 6.8.

Keywords: Poly(acrylic acid); Poly(vinyl pyrrolidone); Mucoadhesive microsphere; Gastric residence time

1. Introduction

In order to develop oral drug delivery systems, it is necessary to optimize both the residence time of the system in the gastrointestinal (GI) tract and the release rate of the active ingredient from the system. One of the most extensively studied methods for prolonging the residence time in the GI tract is using mucoadhesive polymers that adhere to the mucus layer and release the loaded drug in a sustained manner (Lueßen et al., 1994; Wang et al., 2001). The intimate contact of the mucoadhesive polymer with the mucous surface can result in an increased drug retention time and drug concentration in the GI tract (Wang et al., 2001). This should have

* Corresponding author. Tel.: +82 62 230 6367; fax: +82 62 228 3742.
E-mail address: hgchoi@chosun.ac.kr (H.-K. Choi).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.10.016

an improved therapeutic effect for the gastric diseases (Wang et al., 2000; Nagahara et al., 1998). Moreover, mucoadhesive dosage forms have also been reported to improve the absorption and systemic bioavailability of the drugs that are normally poorly absorbed (Nagai and Machida, 1985). While the GI residence time of some of the mucoadhesive dosage forms was not extended in vivo (Khosla and Davis, 1987; Harris et al., 1990), various mucoadhesive microspheres have been successful in extending the GI residence time (Wang et al., 2001; Nagahara et al., 1998). When the mucoadhesive dosage form is administered in either tablet or capsule form, they may or may not adhere to the mucous surface due to the weight of the dosage form and the vigorous movement of the GI tract, resulting in a large variation. However, the mucoadhesive microspheres have some advantages. These include a light weight and a smaller dose variations due to the large number of microspheres administered.

The widely studied mucoadhesive materials include chitosan, hydroxypropyl cellulose, poly(acrylic acid) (PAA) and their derivatives. Although, PAA is considered to be one of the best mucoadhesive polymers, the high water solubility of PAA critically limits its use as a carrier for the sustained release of a drug. PAA based interpolymer complexation (Choi et al., 1999; Chun et al., 2001, 2002a,b) has been examined in order to reduce the water solubility of PAA. In those studies, it was shown that the water solubility of PAA could be reduced and the adhesive force could be maintained via the complexation of the PAA with proton accepting polymers such as poly(ethylene glycol), poly(ethylene glycol) macromer, poloxamer and poly(vinyl pyrrolidone) (PVP) (Choi et al., 1999; Chun et al., 2001, 2002a,b). It was also observed that PAA and PVP aggregate and precipitate in ethanol and water in a relatively short period of time, resulting in the formation of a PVP/PAA interpolymer complex, suggesting that the intensity of hydrogen bonding between PAA and PVP is quite strong. It was believed that this strong complexation could be utilized to prepare mucoadhesive microspheres. Each component is soluble in water. However, when they come together they form a complex and precipitate. If a PAA solution and PVP solution can be emulsified and droplets of each emulsion collides afterwards, complexation should occur, which will solidify to form microspheres.

This study investigated the effect of various preparation parameters on the formation and morphology of microspheres and optimized the preparation conditions for microspheres. In addition, the release of a drug from the prepared mucoadhesive microspheres was examined.

2. Materials and methods

2.1. Materials

The PVP (MW: 42,500) was obtained from BASF (Ludwigshafen, Germany). The PAA (MW: 450,000) was purchased from Aldrich (Milwaukee, WI). Sorbitan monooleate (span 80) was purchased from Junsei Chemical (Tokyo, Japan). Corn oil was acquired from CJ Corporation (Seoul, Korea). All other chemicals were of reagent grade available commercially.

2.2. Methods

2.2.1. Preparation of mucoadhesive microspheres

The mucoadhesive microspheres were prepared by interpolymer complexation and solvent diffusion method. PAA (0.2 g) was dissolved in 4.8 g of ethanol/water (7/3, w/w) mixture and PVP (0.32 g) was dissolved in 1 g of ethanol/water (7/3, w/w) mixture unless otherwise specified. When two solutions were combined together, the concentration of polymer, PAA and PVP, was 8.2%. Using a syringe, the PAA solution and PVP solution were sequentially dropped into 200 ml of corn oil, which was used as the external phase. The external phase contained 0.04% v/v of span 80 (sorbitan monooleate) as a surfactant. They were stirred with a magnetic bar at 500 rpm at an ambient temperature over 36 h. The microspheres were gradually hardened and the hardened microspheres were collected by filtration. They were washed several times with *n*-hexane and dried at 80 °C over 12 h. The yield was calculated by dividing the weight of the collected microspheres by the total weight of all the non-volatile components used for preparing the microspheres.

In order to examine the effect of the amount of internal phase used, the effect of the solvent ratio of the internal phase, the surfactant concentration, and the polymer concentration on the formation of microspheres, each relevant variable was changed with other variables