Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 293 (2005) 63–72
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Carrageenans can regulate the pulmonary absorption of antiasthmatic drugs and their retention in the rat lung tissues without any membrane damage

Keigo Yamada [a, b], Naoki Kamada [b], Masaaki Odomi [b], Naoki Okada [a], Takeshi Nabe [c], Takuya Fujita [a], Shigekatsu Kohno [c], Akira Yamamoto [a, *]

[a] *Department of Biopharmaceutics, Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan*
[b] *Formulation Research Institute, Otsuka Pharmaceutical Co., Ltd., 224-18 Ebisuno Hiraishi Kawauchi-cho, Tokushima 771-0182, Japan*
[c] *Department of Pharmacology, Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan*

Received 11 October 2004; received in revised form 9 December 2004; accepted 11 December 2004

Abstract

Effects of various viscous vehicles on pulmonary absorption of antiasthmatic drugs were examined by an in situ pulmonary absorption experiment. Theophylline and fluticasone propionate were used as antiasthmatic drugs. The serum concentration–time profile of theophylline without viscous vehicles was similar to that following the intravenous injection, indicating that pulmonary absorption of theophylline was rapid and absolute. The serum concentration of theophylline was not controlled in the presence of 5% gelatin or 2% sodium alginate. However, 1% iota-carrageenan could control and regulate the serum concentration of theophylline. In the pharmacokinetic analysis, the C_{max} values of theophylline significantly decreased, and its T_{max} values increased in the presence of 1% and 2% iota-carrageenan, 1% kappa-carrageenan, and 2% sodium alginate compared with the control. The MRT and MAT values of theophylline with 1% iota-carrageenan were significantly higher than those without viscous vehicles. The local concentration of theophylline in the lung at 1 h after intratracheal administration increased five-fold with 1% iota-carrageenan compared with the control. On the other hand, the pulmonary absorption of fluticasone propionate was controlled and regulated in the presence of 0.5% kappa-carrageenan. Additionally, the pulmonary inflammation after the exposure of carrageenans administered to the lung was evaluated in rats. Iota- and kappa-carrageenans did not cause local serious

* Corresponding author. Tel.: +81 75 595 4661; fax: +81 75 595 4761.
E-mail address: yamamoto@mb.kyoto-phu.ac.jp (A. Yamamoto).

0378-5173/$ – see front matter
doi:10.1016/j.ijpharm.2004.12.008

damage and inflammation to the pulmonary tissue. Therefore, these findings indicated that the carrageenans were effective to regulate the absorption rate of antiasthmatic drugs including theophylline and fluticasone propionate.

Keywords: Pulmonary absorption; Viscosity; Carrageenan; Mucoadhesion; Controlled release; Pulmonary inflammation

1. Introduction

The large surface area of the alveolar epithelium and the short distance of the air-blood pathway are unique features of the lung that can facilitate systemic delivery alternative for delivering therapeutic proteins and peptides (O'Hagan and Illum, 1990; Agu et al., 2001). Actually, pulmonary absorption of these proteins and peptide drugs which are poorly absorbed from the gastrointestinal tract, was observed (Enna and Schanker, 1972a; Wigley et al., 1971). Moreover, the bioavailability of these drugs was significantly improved by co-administration with various adjuvants such as absorption enhancers and protease inhibitors (Okumura et al., 1992; Komada et al., 1994; Kobayashi et al., 1994; Morita et al., 1994; Yamamoto et al., 1994, 1997, 2001; Todo et al., 2001). However, rapid pulmonary absorption of these peptides, especially insulin may cause hypoglycemic events and other serious side effects. Consequently, the control of pulmonary absorption rate of drugs is very important for therapeutic effects and safety of the drugs.

On the other hand, recently, chronic obstructive pulmonary disease (COPD) is a major public health problem and it is the fourth leading cause of chronic morbidity and mortality throughout the world (WHO, 2000). Moreover, nocturnal and early morning wheezing is very common in asthmatics. The clinical importance of this symptom is underlined by the fact that the majority of deaths from asthma and many episodes of ventilatory arrest occurred in the early morning (Barnes et al., 1980; Kiyokawa et al., 1999). Therefore, the local acting drugs including antiasthmatic agents, bronchodilators and expectorants should be localized for a long period in the lung tissues. Nevertheless, few studies have been examined to control and regulate the absorption rate of such drugs after intrapulmonary administration (Morimoto et al., 2001).

In a previous study, effect of various viscous vehicles on the pulmonary absorption of water-soluble drug, 5(6)-carboxyfluorescein (CF) was examined by an in situ pulmonary absorption experiment. Consequently, viscous vehicles, especially 5% gelatin and 1% PVA, were effective to control the pulmonary absorption of CF, a water-soluble drug with low molecular weight and they might be useful to increase the local concentration of drugs in the lung (Yamamoto et al., 2004).

Carrageenan is a generic term for naturally occurring polysaccharides that fill the void spaces in the cellulose backbone structures in certain species of red seaweed. The use of carrageenan extends back to ancient times and carrageenans are widely utilized due to their excellent physical functional properties such as thickening, gelling, and stabilizing abilities in the current food industry (Ikeda, 2003). Moreover, carrageenans are used as an excipient for the pharmaceutical formulation. However, few studies have been reported the effect of carrageenans on the control and regulation of pulmonary absorption of drugs, especially antiasthmatic drugs.

In this study, theophylline and fluticasone propionate were chosen as antiasthmatic drugs, and the effects of various viscous vehicles including gelatin, iota-, kappa-carrageenan, sodium alginate on the absorption of the drugs after intrapulmonary administration were examined in rats. Additionally, the pulmonary inflammation after the exposure of carrageenans administered to the lung was evaluated in rats.

2. Materials and methods

2.1. Materials

Theophylline was purchased from Shiratori Pharmaceutical Co. (Chiba, Japan). Fluticasone propionate was purchased from Sicor S.p.A. (Perugia, Italia). Gelatin and sodium alginate were obtained from Nacalai Tesque Inc. (Kyoto, Japan) and Wako Pure Chemical Industries, Ltd. (Osaka, Japan), respectively. Iota-, lambda- and kappa-carrageenans were purchased