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Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use

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Abstract

To develop the suitable film formulations of propranolol hydrochloride (PPL) containing enhancers for transdermal use, polymeric film formulations were prepared by employing ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) as a film former, and dibutyl phthalate (DBP) as a plasticizer. Terpenes such as menthol and cineole, and propylene glycol (PG) were also employed as a chemical enhancer to improve the skin penetration of PPL. The film preparations were characterized in physical properties such as uniformity of drug content, thickness and moisture uptake capacity. Release and skin permeation kinetics of PPL from film preparations were examined in the in vitro studies using a Franz-type diffusion cell. The uniformity of drug content was evidenced by the low S.D. values for each film preparation. The moisture uptake capacity and drug release rate increased with the increase of PVP in each preparation. Enhancers examined in the present study also increased the moisture uptake capacity and release rate of PPL from the film preparations. Increasing the concentration of PPL from 1 to 2 mg/cm^2 in the film enhanced the release rate of PPL, while no effect of enhancer concentrations on the release rate from the film preparations was observed. In vitro skin permeation study showed that cineole was the most promising enhancer among the enhancers examined in the present study and suggested that the suitable compositions of film preparation would be EC:PVP:PPL = 6:3:4 with 10% (w/w) cineole and 7:2:4 with 10% (w/w) PG and cineole, which provided high skin permeation rates at 93.81 ± 11.56 and 54.51 ± 0.52 μg/cm^2/h, respectively.

Keywords: Propranolol hydrochloride; Terpene; Transdermal absorption; Polymeric film; Cineole; Propylene glycol

1. Introduction

Oral administration is one of the most convenient ways that are acceptable for patients, useful and suitable for some drugs that are not subjected to intestinal

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and/or hepatic first-pass metabolism (Kimura and Higaki, 2002). However, there are several disadvantages that should be overcome for achieving the efficient drug therapy as follows: the intestinal and/or hepatic first-pass elimination, high variance in bioavailability due to variable condition of gastrointestinal tract, difficulty in long-term and rate-regulated absorption and impossibility of arbitrary drug input and its interruption (Higaki et al., 2003). Transdermal route is one of the potent alternative routes that can improve undesirable characteristics of oral administration. Particularly, as propranolol, a β-blocker, has a short biological half-life and is subjected to extensive hepatic first-pass metabolism (Walle et al., 1979; Sawamoto et al., 1997), propranolol must be a potential candidate for the transdermal use. Recently, development of transdermal drug delivery systems (TDDS) has been focused on the formulation that can achieve the desirable constant rate of drug penetration into the systemic circulation, especially by employing several polymers as matrices or membranes controlling the release of drugs (Kou, 2000). On the other hand, the impermeability of human skin is still a fundamental problem to be overcome for the therapeutic use of TDDS (Barry, 2001a). Although many approaches have been proposed to overcome the stratum corneum, a main barrier for transdermal drug absorption (Higaki et al., 2003), chemical approaches such as a utilization of chemical enhancers might be only applicable to patch preparations. Among many enhancers examined, terpenes have been extensively investigated for their clinical use as an penetration enhancer and suggested to increase drug diffusivity in the skin by disrupting the intercellular lipid packing in the horny layer (Vaddi et al., 2002; Higaki et al., 2003). Considering the balance between efficiency and toxicity, several terpenes may be promising chemical enhancers for clinical use (Kitahara et al., 1993; Higaki et al., 2003). In the present study, we tried to develop a suitable film preparation of propranolol hydrochloride (PPL) by employing ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) as a film former, and dibutyl phthalate (DBP) as a plasticizer. Furthermore, in order to improve the penetration of PPL, terpenes such as menthol and cineole, and propylene glycol (PG) were employed as a chemical enhancer. Release and permeation profiles of PPL from film preparations were examined in the in vitro studies using a Franz-type diffusion cell.

2. Materials and methods

2.1. Materials

EC (with an ethoxy content 47.5–53.5% by weight and a viscosity of 9–11 cps in a 5% (w/w), 80:20 toluene/ethanol solution at 25 °C, Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), PVP K30, DBP, chloroform (HPLC grade) and cineole were obtained from Nacalai Tesque (Kyoto, Japan). PPL, PG and menthol were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Other chemicals obtained commercially were of a reagent grade.

2.2. Animals

Male Wistar rats (Japan SLC, Hamamatsu, Japan), maintained at 25 °C and 55% humidity were allowed free access to standard laboratory chow (Clea Japan, Tokyo) and water prior to the experiments. Rats weighing 150–200 g were randomly assigned to each experimental group. Our investigations were performed after approval from the local ethical committee at Okayama University and in accordance with ‘Interdisciplinary Principles and Guidelines of the Use of Animals in Research’.

2.3. Preparation of film formulations containing PPL

Films composed of different ratios of EC, PVP, enhancers and PPL were prepared by a method reported previously (Kurosaki et al., 1988). All the ingredients were weighed in requisite ratio and they were then dissolved in 25 ml of chloroform. DBP was incorporated at a concentration of 30% (w/w) of dry weight of polymers as a plasticizer. An enhancer was dissolved at a concentration of 5% or 10% (w/w) of total dry weight of EC, PVP and DBP. The resultant chloroform solutions were poured into a Teflon tray, and were dried at 45 °C for 12 h.

2.4. Film thickness

The thickness of films was measured at three different places using a micrometer (Mitutoyo Co., Kanagawa, Japan) and mean values were calculated.