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Oral solid gentamicin preparation using emulsifier and adsorbent

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Abstract

Oral gentamicin (GM) therapy has been challenged by formulating GM in oral solid preparation. GM was dispersed with a surfactant used for the self-microemulsifying drug delivery system (SMEDDS), PEG-8 caprylic/capric glycerides (Labrasol), and the mixture was solidified with several kinds of adsorbents. The used adsorbents were microporous calcium silicate (Florite™ RE), magnesium alminometa silicate (Neusilin™ US_2), and silicon dioxide (Sylysia™ 320). In vitro release study showed that the percentage released of GM from each preparation per 2 h was $99.8 \pm 0.06\%$ for Florite RE 10 mg, $96.7 \pm 1.16\%$ for Florite RE 20 mg, $98.3 \pm 0.32\%$ for Neusilin US_2, and $94.4 \pm 0.23\%$ for Sylysia 320. The $T_{50\%}$ values were 0.35 ± 0.05 h for Florite RE 10 mg, 0.34 ± 0.03 h for Florite RE 20 mg, 0.26 ± 0.03 h for Neusilin US_2, and 0.15 ± 0.01 h for Sylysia 320. The in vivo rat absorption study showed that Florite RE 10 mg preparation had the highest C_{max} (2.14 ± 0.67 μg/ml) and AUC (4.74 ± 1.21 μg h/ml). Other preparations had C_{max} and AUC of 0.69 ± 0.10 μg/ml and 1.56 ± 0.43 μg h/ml for Florite RE 20 mg, 1.07 ± 0.31 μg/ml and 1.80 ± 0.33 μg h/ml for Neusilin US_2, and 0.99 ± 0.21 μg/ml and 1.77 ± 0.50 μg h/ml for Sylysia 320, respectively. The bioavailability (BA) of GM from the microporous calcium silicate preparation, Florite RE 10 mg, was 14.1% in rats, derived by comparing the AUC obtained after intravenous injection of GM, 1.0 mg/kg, to another group of rats. The microporous calcium silicate preparation using Florite RE 10 mg was evaluated in dogs after oral administration in an enteric capsule, Eudragit S100 (50 mg/dog). High plasma GM levels were obtained (i.e., the C_{max} was 1.26 ± 0.20 μg/ml and the AUC was 2.59 ± 0.33 μg h/ml). These results suggest that an adsorbent system is useful as an oral solid delivery system of poorly absorbable drugs such as GM.
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Keywords: Gentamicin sulfate (GM); Labrasol; Adsorbent; Microporous calcium silicate; Magnesium alminometa silicate; Silicon dioxide; Absorption enhancement

1. Introduction

GM is an important antibacterial agent for the treatment of a wide variety of Gram-negative bacilli

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and Gram-positive cocci infections [1,2]. However, its clinical use is limited to injection or topical dosage forms. In the case of intravenous (i.v.) therapy, many problems are associated with the use of GM in injection form (i.e., low quality of life (QOL) of the patients resulting in the inconvenience of injections for long-term administration). Parenteral administration of GM has been associated with side effects that include mainly nephrotoxicity and ototoxicity [3–5].

Many scientists have been challenged to develop new dosage forms of GM to solve these problems. Alternative administration route, such as via nasal mucosa for systemic therapy, would improve QOL in patients. However, it was also observed that GM has poor transmucosal permeability [6,7]. Therefore, we have been studying an oral delivery system to develop nonparenteral GM preparation, although GM is a representative poorly absorbable drug from the gastrointestinal (GI) tract. As GM is a polar water-soluble compound, it is commonly recognized that intestinal membrane permeability of GM is poor. Therefore, GM has a low oral BA [8]. According to the classification of drugs having low BA, proposed by Amidon et al. [9], GM belongs to class III compounds (high solubility and low membrane permeability) of the biopharmaceutical classification system (BCS).

In our previous report, the BA of GM was greatly increased by formulating GM in a self-microemulsifying drug delivery system (SMEDDS) using PEG-8 caprylic/capric glycerides (Labrasol). Labrasol contains saturated polyglycolysed C_6–C_{14} glycerides, where C_8 is 58.1% and C_{10} is 39.8%. Labrasol is a safe pharmaceutical additive; namely, it shows high tolerance and low toxicity for animals. LD_{50} is 22.0 g/kg for rats and is a surfactant listed in the European Pharmacopoeia. SMEDDS is expected to self-emulsify rapidly in the aqueous environment in the small intestine, thereby presenting the drug in solution in small droplets of oil. The gentle agitation required for the emulsification is provided by the digestive motility of the small intestine. By formulating GM in Labrasol SMEDDS, a high BA value of GM, approximately 55%, was obtained after administration to the rat's small intestines [10]. The dosage form that results from SMEDDS is usually either a liquid or liquid filled into soft gelatin capsules. However, from the standpoint of pharmaceutics, solid dosage form is preferred than liquid preparation because of cost performance and convenience for the manufacturing process. Therefore, an alternative dosage form that can incorporate SMEDDS into a powder to produce a solid dosage form has been challenged, and prepared solid dosage forms have been evaluated both in rats and dogs.

2. Materials and methods

2.1. Materials

Gentamicin sulfate (GM) was obtained from Nacalai Tesque, Inc. (Kyoto, Japan). PEG-8 caprylic/capric glyceride (Labrasol) (Gattefösse, Lyon, France) was a gift from Chugai Boyeki Co., Ltd. (Tokyo, Japan). Eudragit® S100 (Röhm Pharm, Darmstadt, Germany) was obtained through Higuchi, Inc. (Tokyo, Japan). Polysorbate 80 (commonly called Tween 80) was obtained from Nacalai Tesque, Inc. (Kyoto, Japan). *O*-phthalaldehyde (OPA) was obtained from Ishizu Seiyaku, Ltd. (Osaka, Japan). Magnesium aluminometa silicates (Neusilin™ US_2) were obtained from Fuji Chemical Industry Co., Ltd. (Toyama, Japan). Porous silicon dioxide (Sylysia™ 320) was obtained from Fuji Silysia Co., Ltd. (Aichi, Japan). Porous calcium silicate (Florite™ RE) was obtained from Eisai Co., Ltd. (Tokyo, Japan). Acetonitrile was of HPLC grade. All other reagents were of analytical reagent grade and were used as received. Male Wistar rats used in the study and standard solid meal of commercial food (LabDiet®) were obtained from Nippon SLC Company (Hamamatsu, Japan). Male beagle dogs (10.0–12.5 kg) used in this study and standard solid meals of commercial food (Labo D stock®) were obtained from Nippon Nousan Co., Ltd. (Yokohama, Japan).

2.2. Preparation for absorption study

GM sulfate, 74.29 mg (equivalent to 50 mg of GM), was well suspended with 0.6 ml of Labrasol; thereafter 100 mg or 200 mg of Florite RE, 300 mg of Neusilin US_2, or 200 mg of Sylysia 320 was added. By kneading well, solid preparation was obtained as shown in Table 1. In the case of dog study, an enteric capsule (size #000) was prepared by rolling a Eudragit

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