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Oral sustained-release suspension based on a lauryl sulfate salt/complex

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ABSTRACT

The objective of this study was to evaluate the feasibility of lauryl sulfate (LS) salt/complex as a novel carrier in oral sustained-release suspensions. Mirabegron, which has a pH-dependent solubility, was selected as the model drug. Sodium lauryl sulfate (SLS) was bound to mirabegron in a stoichiometric manner to form an LS salt/complex. LS salt/complex formulation significantly reduced the solubility of mirabegron and helped mirabegron achieve sustained-release over a wide range of pH conditions. Microparticles containing the LS salt/complex were prepared by spray drying with the aqueous dispersion of ethylcellulose (Aquacoat® ECD). The diameter of the microparticles was less than 200 μm, which will help avoid a gritty taste. In vitro results indicated the microparticles had slower dissolution profiles than the LS salt/complex. The dissolution rate could be controlled flexibly by changing the amount of Aquacoat® ECD. The microparticle suspension retained the desired sustained-release property and dissolution profile after being stored for 30 days at 40 °C. In addition, the suspension displayed sustained-release behavior in dogs without a pronounced C_{max} peak, which will help prevent side effects. These results suggest that microparticles containing LS salt/complex may be useful as a novel sustained-release suspension for oral delivery.

1. Introduction

Oral sustained-release dosage forms have been developed in an attempt to improve patients' quality of life by reducing the inconvenience caused by frequent administration of conventional dosage forms. The majority of hydrophilic drugs, if not formulated properly, readily release drug at a fast rate and are likely to produce toxic concentrations when administered orally. Sustained-release formulations can maintain the constant therapeutic levels for a longer period of time and reduce the fluctuations in plasma drug concentrations. Among sustained-release dosage forms, multiple unit dosage forms are preferred over single unit systems because of their better predictability, reproducible therapeutic effects, and less frequent side effects (Porter and Bruno, 1990). Multiple unit dosage forms are more uniformly distributed in the gastrointestinal tract resulting in more reproducible drug release profiles, more predictable gastric emptying, homogeneous drug absorption, and reduced local irritation. They also minimize the risk of dose dumping and avoid unwanted intestinal retention of the polymeric material.

Multiple unit dosage forms offer the possibility of liquid suspension formulations. Oral liquids are often useful for pediatric and geriatric patients or for patients who have difficulty swallowing. Liquid suspensions are more flexible for dose adjustment (Frichman, 1993). Syrup-based oral liquid is generally the preferred dosage form; however, formulating syrup-based liquids to have sustained-release properties can be challenging owing to the diffusion or release of drug into the suspending vehicle during storage, which often results in unwanted changes to the original properties. The amount of drug leakage into the storage vehicle is mainly determined by the solubility of the drug in the vehicle. Therefore, multiple unit dosage forms containing water-insoluble drugs are useful because they can be suspended

Abbreviations: LS, lauryl sulfate; SLS, sodium lauryl sulfate; SEM, scanning electron microscopy; SD, standard deviation; C_{max}, maximum concentration; t_{max}, time to reach C_{max}; AUC, area under the curve.

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into aqueous vehicles without significant drug leaching during storage (Bodmeier and Chen, 1989; Kawashima et al., 1991; Lewis et al., 1998; Khan et al., 2010; Kawano et al., 2010). In contrast, encapsulated water-soluble drugs diffuse rapidly into aqueous suspending vehicles. To overcome this problem, an ion-exchange resin can be used for water-soluble drugs to form a reversible complex, offering one of very few usable systems for achieving ready-to-use aqueous liquid products with prolonged-release (Borodkin, 1993; Varaporn and Greepol, 2008; Sivaneswari et al., 2016). However, ion-exchange resins are often costly and could not singly achieve adequate sustained release of tested drugs at various pH levels. With sustained-release dosage forms, drug release in vitro should preferably be independent of the pH of the release medium in order to minimize biopharmaceutical variability (Varma et al., 2005).

This challenging issue can potentially be overcome by using lauryl sulfate (LS) salt/complex with an adequate sustained-release at various pH conditions. Sodium lauryl sulfate (SLS) is an anionic surfactant with excellent wetting properties across a wide range of pH and is used for many pharmaceutical and cosmetic applications (Shokri et al., 2008; Wang et al., 2005; Woo et al., 2007). SLS is a Generally Regarded as Safe (GRAS) chemical and is included in the FDA Inactive Ingredients Guide (dental preparations; oral capsules, suspensions, and tablets; topical and vaginal preparations), in the list of nonparenteral medicines licensed in the UK, and in the Canadian List of Acceptable Non-Medicinal Ingredients (Rowe et al., 2005). It has been used as a solubilizer to improve the solubility and dissolution rate of cyclosporine A (Lee et al., 2001). SLS has also been reported to form salts/complexes between lauryl sulfate (LS) anions and protonated drug forms (Bhattachar et al., 2011; Jain et al., 2004). LS salt/complex has been utilized to increase the lipophilicity of insulin (Dai and Dong, 2007; Matsuura et al., 1993) and to enhance bioavailability of the poorly absorbed RWJ-445167 compound within an in situ gelling formulation (Dai et al., 2013). We have previously reported that LS salt/complex bound with mirabegron significantly reduced mirabegron solubility and helped mirabegron achieve sustained-release over a wide range of pH conditions (Kasashima et al., 2016). However, the application of LS salt/complex for suspension has not yet been evaluated. The present objective of this study was to prepare the sustained-release suspension using LS salt/complex, and evaluate its dissolution stabilities at 25 °C, which is an average room temperature of, and at accelerated temperature of 45 °C. Furthermore, the in vivo adsorption and bioavailability of the suspension were compared to that of mirabegron solution in dogs under fasted and fed conditions.

2. Materials and methods

2.1. Materials

Mirabegron, 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-(2-ethyl)phenyl]acetamide, was used as the model drug; its solubility is pH-dependent (pH 1, 12933.0 μg/mL; pH 3, 501.4 μg/mL; pH 6, 116.1 μg/mL) and its pharmacokinetics are affected by the presence or absence of food (Takaishi et al., 2010; Kasashima et al., 2016). Mirabegron is a β_3-adrenergic receptor agonist used for the treatment of overactive bladder (Herschorn et al., 2013; Khullar et al., 2013; Nitti et al., 2013). Mirabegron was provided by Astellas Pharma Inc. (Tokyo, Japan). SLS was purchased from Cognis GmbH (Monheim, Germany). Aqueous colloidal dispersion of ethylcellulose (Aquacoat® ECD) was purchased from FMC (DE, USA). Triethyl citrate (TEC) was purchased from Pfizer (Citrofrex®2; Pfizer K.K., Tokyo, Japan). All other chemicals were of reagent grade.

2.2. Methods

2.2.1. Preparation of LS salt/complex

LS salt/complex was prepared according to the method described in previous study (Kasashima et al., 2016). Mirabegron was dissolved in 0.1 N HCl (50.4 mM) and SLS was dissolved in purified water (100.9 mM). The SLS solution was mixed into the mirabegron solution (2:1 SLS/mirabegron molar ratio) with a propeller agitator. The solution became cloudy and a white precipitate formed. The white precipitate, LS salt/complex, was separated by aspirating filtration and dried at 40 °C for 12 h. After drying, the LS salt/complex was delumped through a 1000-μm screen with an impeller at 3450 rpm using a power mill (Showa Kagaku Kikai Co. Ltd., Japan). It was then further dried at 40 °C for 12 h. After that, the LS salt/complex was pulverized with a pin-type screw at 11200 rpm using a fine impact mill (100 UPZ, Hosokawa Micron Ltd., Japan).

2.2.2. Microparticles containing LS salt/complex

Sustained-release microparticles containing LS salt/complex were prepared by spray drying method using the formula shown in Table 1. An Ohkawara Kakohki L-8 spray dryer (Ohkawara Kakohki Co., Ltd., Japan) with a rotary disc atomizer was used. The suspension for spray drying was prepared with pulverized LS salt/complex suspended in Aquacoat® ECD containing the plasticity agent TEC (4.3% of coat, w/w). The suspension was stirred for 3 h and was sieved through a 250-μm sieve prior to spray drying. The drying was performed using the following parameters: inlet temperature 104 °C to 110 °C, outlet temperature 82 °C to 91 °C, spray rate 30 g/min, and atomizer rotation speed 10000 rpm. The feeding suspension was mixed continuously during the drying process using a magnetic stirrer to prevent sedimentation of the suspended LS salt/complex. The spray dried microparticles were collected from the aero cyclone and cured for 4 h at 70 °C in a drying chamber (DN-910, Yamato Scientific Co. Ltd., Japan).

2.2.3. Scanning electron microscopy

Morphological characteristics of the LS salt/complex and the microparticles containing LS salt/complex were studied using a scanning electron microscope (SEM) (VHX-D510, KEYENCE, Japan).

2.2.4. Particles size distribution

Particles size distribution was determined by measuring microparticles (5 g) using the sieve method (Robot Sifter, Seishin Enterprise Co. Ltd., Japan). Screens with openings of 63, 75, 106, 150, 180, 250, 355, and 500 μm were used to separate each fraction. The average particle size (median diameter) was estimated from the weight of the fraction based on percentage cumulative curves.

2.2.5. In vitro dissolution studies

The dissolution studies were performed in accordance with Dissolution Test Method 2 (paddle method), as cited in the

Table 1
Composition of prepared microparticles.

Component	Formulation		LS salt/complex (Reference)
	A	B	
Mirabegron	25	25	25
SLS	36.5	36.5	36.5
Aquacoat® ECD	50	100	–
TEC	7.5	15	–
Total (mg)	119	176.5	61.5