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Development of a gastric retentive system as a sustained-release formulation of pranlukast hydrate and its subsequent *in vivo* verification in human studies

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ABSTRACT

Pranlukast hydrate was demonstrated in a human site-of-absorption study to have extremely poor absorption properties in the lower gastrointestinal tract. The ratios of AUC0-24 in the distal small bowel and colon compared to stomach delivery were approximately 1/7 and 1/70, respectively. As a consequence, a gastroretentive double-layered tablet formulation (gastric swelling system; GSS), consisting of a swelling layer and a drug release layer, was developed for once-daily dosing. To study the gastric retention of the optimized GSS, an *in vivo* gamma scintigraphic study was carried out in nine healthy volunteers. The transit profiles demonstrated that the GSS was retained in the stomach for more than 10 h. The plasma profile was prolonged, especially following administration after an evening meal. The human data validated the design concept and suggest that GSS could be a promising approach for the development of sustained-release formulation for drugs with a limited absorption window in the upper small bowel.

1. Introduction

Pranlukast hydrate is a specific leukotriene receptor antagonist used for the treatment of asthma. It selectively binds to and blocks the action of leukotriene receptors, which are closely related to the basic pathogenesis of bronchial asthma. ONON® capsules (112.5 mg pranlukast hydrate) have been marketed in Japan since 1995 as a first line treatment for adult bronchial asthma. Since their launch, additional indications have been added and new drug applications have been filed for allergic rhinitis and childhood asthma. ONON® capsules have to dosed twice-a-day to achieve efficacious drug concentrations in the plasma for 24 h due to Pranlukast's short plasma half-life (1.2 h); however, two other products, SINGULAIR® (Merck) and ACCOLATE® (AstraZeneca), have also been launched. SINGULAIR® (montelukast sodium) has a long plasma half-life and is therefore dosed once daily. Therefore, in terms of life cycle management, a once-daily dosage form of pranlukast hydrate would be highly desirable.

One option to overcome the short plasma half-life and develop a once-daily product is the development of a sustained-release formulation. However, sometimes sustained-release formulations fail to accomplish a sufficient duration of *in vivo* absorption. One reason for this is that although colonic residence for the formulation is extended, the available volume of water for drug dissolution is very limited and the region can have low permeability. Pranlukast hydrate has an extremely poor aqueous solubility in water and poor permeability properties, with the result that it has been classified as a BCS IV compound. Therefore, the extent of colonic absorption should be assessed to ensure a rational formulation design. The assessment of regional absorption utilizing animals is controversial due to the lack of correlation between humans and animals with respect to drug absorption (Grass and Sinko, 2001). Ideally, therefore, colonic drug absorption issues should be addressed in human studies (Wilding, 2004).

Gastric retentive drug delivery technologies provide an innovative option in the field of oral controlled-release by overcoming issues around a limited drug absorption window. Furthermore, gastric retentive extended-release formulations could maximize the duration of drug absorption from the upper gastrointestinal tract and hence compensate for the short half-life of pranlukast. There are three main technological approaches: mucoadhesion, where the dosage form adheres to the stomach or intestinal walls such that motility is limited; floatation, where the dosage form cannot leave the stomach because of its orientation to the pylorus;

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and expansion, where the dosage form becomes too large to pass through the pyloric sphincter. Although there have been many clinical studies examining gastric retentive drug delivery systems that utilize mucoadhesion (Khosla and Davis, 1987; Harris et al., 1990; Jackson et al., 2001; Säkkinnen et al., 2003, 2004), floatation (Ingani et al., 1987; Agyilirah et al., 1991; Kawashima et al., 1991; Phuapradit and Bolton, 1991; Hilton and Deasy, 1992; Oth et al., 1992; Timmermans and Moës, 1994; Atyabi et al., 1996; Whitehead et al., 1998; Gabr and Borg, 2000; Swicki, 2002; Chavanpatil et al., 2005) and expansion (Fix et al., 1993; Gusler et al., 2001; Klausner et al., 2003), there remain very few commercial products, i.e., only GLUMETZA® tablets (metformin hydrochloride; Depomed Inc.), GRALISE® tablets (gabapentin; Depomed Inc.) and JANUMET® XR (sitagliptin and metformin HCl; Depomed Inc.). Based on the limited number of available commercial products, a gastric retentive system is not an established technology and therefore designing an appropriate formulation can be considered an uncertain and challenging strategy.

The aim of this program of work was to evaluate the regional drug absorption of the poorly soluble pranlukast hydrate in humans, to develop a gastric swelling system (GSS) of pranlukast hydrate in order to achieve once-daily administration, and to evaluate the formulation concept in humans. Verification of improved *in vivo* performance was achieved by combining drug plasma concentration profiling and scintigraphic analysis of transit in healthy human subjects.

2. Materials and methods

2.1. Materials

Pranlukast hydrate (molecular weight; 490.51, melting point; 231–235 °C) was synthesized by Ono Pharmaceutical Co., Ltd. Hydroxypropyl methylcellulose (HPMC 90SH-100 and 4000; Shin-Etsu Chemical Co., Ltd., Japan) and methacrylic acid copolymer (EUDRAGIT® L 100-55; Evonik Industries AG, Germany) were used as release controlling agents. Xanthan gum (Echogum T; Dainippon Sumitomo Pharma Co., Ltd. Japan), guar gum (KT-0104; Dainippon Sumitomo Pharma Co., Ltd., Japan) and hydroxypropyl methylcellulose (HPMC 90SH-30000F and 400; Shin-Etsu Chemical Co., Ltd., Japan) were used as swelling control agents. Samarium oxide (^{152}Sm; CK Gas Products, UK) was used as a precursor to the radioactive tracer. Hydroxypropyl cellulose (HPC-SSL; Nippon Soda Co., Ltd., Japan) was used as a binder. Magnesium stearate (Taihei Chemical Industrial Co., Ltd., Japan) was used as a lubricant. Lactose (Carter Holt Harvey, Ltd., New Zealand) and microcrystalline cellulose (Avicel PH-101; Asahi Kasei Chemicals Co., Japan) were used as non-functional excipients. All the other ingredients and excipients used met the Japan pharmacopoeial requirements or were of analytical grade.

2.2. Manufacture of the gastric swelling system (GSS)

2.2.1. Manufacture of a swelling layer for in vitro swelling tests

Xanthan gum (40%, w/w), HPMC 90SH-400 (23.3%, w/w), guar gum (6.7%, w/w), lactose (20.0%, w/w) and microcrystalline cellulose (10.0%, w/w) were mixed and used as the tableting powder for the GSS6 swelling layer. Xanthan gum (40%, w/w), HPMC 90SH-30000F (35%, w/w), guar gum (16.7%, w/w), microcrystalline cellulose (7.8%, w/w) and magnesium stearate (0.5%) were mixed and used as the tableting powder for the GSS12 and 24 swelling layer. The die was filled with tableting powder, and the powder was compressed into tablets each weighing 200 mg using a tableting machine (WPM-2; Toyo Material, Japan) with punches of 8 mm diameter.

2.2.2. Manufacture of GSS12 and GSS24 for human pharmacoscintigraphic and pharmacokinetic studies

Pranlukast hydrate (81.6%, w/w), lactose (10.2%, w/w) and HPC-SSL (8.2%, w/w) were suspended in water and the mixture was granulated by spray drying (L-8 Spray drier; Ohkawara Kakohki Co., Ltd., Japan). A mixture of the spray dried pranlukast hydrate (pranlukast SD), HPMC 90SH-100 for GSS12 or HPMC 90SH-4000 for GSS24, methacrylic acid copolymer (Eudragit L100-55) and lactose was admixed in a fluidized bed granulator (GPCG-1; Glatt, Germany). The resulting mixture was granulated by spraying a solution of HPC-SSL (5%) as binder. The resultant granules were dried, blended with magnesium stearate, and used as the tableting powder for the drug release layer. Xanthan gum, HPMC 90SH-30000F, guar gum, microcrystalline cellulose, samarium-152 oxide and magnesium stearate were mixed, and used as a tableting powder for the swelling layer.

The manufacture of the GSS bilayer tablets consisted of two steps. First, the die was filled with tableting powder for the drug release layer and partially compressed, and then the die was filled with tableting powder to form the swelling layer over the drug release layer, and the powder was compressed into tablets using a tableting machine (TAB-ALL; Okada Seiko Co., Ltd., Japan) with punches of 17.5 × 7.5 mm. The tablet compositions are shown in Table 1. Each tablet contained 225 mg pranlukast hydrate. These formulations were manufactured in accordance with Good Manufacturing Practices (GMP) as required by the ICH Guidelines for Good Clinical Practice (GCP).

2.3. In vitro studies

2.3.1. In vitro swelling studies

The properties of the swelling layer for the GSS6 and GSS12/24 formulations were evaluated by shaking with glass beads added to the dissolution medium. The swelling layer was added to 15 mL of first fluid (pH 1.2), as described for disintegration tests in the Japanese Pharmacopoeia, 16th edition (JP 16), containing 30 g of large glass beads (diameter 10 mm) and 6 g of smaller glass beads (diameter 5 mm), and shaken at 180 strokes/min for 3 h (Taiyo Recipro Shaker SR-2; Taiyo Co., Ltd., Japan). The weight of the swelled tablet layer was measured and the swelling ratio was calculated using the following equation:

$$\text{Swelling ratio}(\%) = \frac{\text{weight of tables after 3 h}}{\text{Initial weight of tablet}} \times 100$$

2.3.2. In vitro drug release studies

The drug release studies were performed according to the JP 16 paddle method. The release medium was 900 mL of first fluid

Table 1
Composition of the tablets evaluated in the healthy volunteer study.

	Component	Quantity (mg/tablet)	
		GSS12	GSS24
Drug release layer	Pranlukast SD	274.3	274.3
	HPMC 90SH-100	112.5	–
	HPMC 90SH-4000	–	112.5
	Methacrylic acid copolymer	31.5	31.5
	Lactose	6.7	6.7
	HPC-SSL	16.0	16.0
	Mg–St	9.0	9.0
Swellable layer	Xanthan gum	120.0	120.0
	HPMC 90SH-30000F	105.0	105.0
	Guar gum	50.0	50.0
	Microcrystalline cellulose	23.5	23.5
	Samarium oxicide	10.0	10.0
	Mg–St	1.5	1.5
	Total	760.0	760.0