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Design and evaluation of an extended-release matrix tablet formulation; the combination of hypromellose acetate succinate and hydroxypropylcellulose

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ABSTRACT

The purpose of this study was to develop an extended-release (ER) matrix tablet that shows robust dissolution properties able to account for the variability of pH and mechanical stress in the GI tract using a combination of enteric polymer and hydrophilic polymer. Hypromellose acetate succinate (HPMCAS) and hydroxypropylcellulose (HPC) were selected as ER polymers for the ER matrix tablet (HPMCAS/HPC ER matrix tablet). Oxycodone hydrochloride was employed as a model drug. Dissolution properties of the HPMCAS/HPC ER matrix tablets were evaluated and were not affected by the pH of the test medium or paddle rotating speed. In a USP apparatus 3 (bio-relevant dissolution method), dissolution profiles of the HPMCAS/HPC ER matrix tablets containing oxycodone hydrochloride were similar to that of the reference product (OxyContin). Moreover, *in vivo* performance after oral administration of the HPMCAS/HPC ER matrix tablets to humans was simulated by GastroPlus based on dissolution profiles from the USP apparatus 3. The plasma concentration-time profile simulated was similar to that of the reference product. These results suggest that the combination of HPMCAS and HPC shows a robust dissolution profile against pH and paddle rotating speed and indicates the appropriate extended-release profile in humans.

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1. Introduction

Extended-release (ER) dosage forms undergo transit in the gastrointestinal (GI) tract after oral administration and the drug is dissolved by degrees. The drug dissolution rate of oral ER dosage form is sometimes affected by composition of GI fluids (pH and bile salts) and the hydrodynamic conditions in the GI tract [1,2]. For oral ER dosage forms, the effects of agitation intensity and mechanical impact force expected in the GI tract, such as contraction or peristalsis, have been investigated [3,4]. Also, it is well known that both physical pH and motility in the GI tract are highly variable among individuals [5–7]. Therefore, the drug release of oral ER dosage forms is required to show robustness accounting for the variability of pH and mechanical stress in the GI tract [8]. It is also important to avoid dose dumping after oral administration of ER dosage forms, especially for drugs which possess the characteristics of a higher solubility, higher dose or a fatal side effect [9,10]. Furthermore, an alcohol-induced dose dumping effect in oral ER dosage forms has gained increased attention in recent years [11,12]. Therefore, the understanding of *in vitro* drug release properties is of great importance to the development of oral ER dosage forms when considering the *in vivo* performance.

Recently, several attempts have been made to develop an ER matrix tablet that shows robust dissolution properties [9,10]. For example, the AcroContin delivery system, which is applied to OxyContin (oxycodone hydrochloride ER matrix tablet), is a single unit system basically consisting of two hydrophobic polymers (ammonio methacrylate copolymers) and shows robust dissolution properties for pH in the GI tract [13,14]. In some articles evaluating ER matrix tablets, a single polymer or a combination of several polymers was used to not only control the drug release but also avoid the effects of mechanical stress [15]. In this study we have focused attention on the characteristics of an enteric polymer and how its pH dependent solubility may overcome mechanical stress in the stomach (acidic condition) by maintenance of the tablet shape of the ER matrix tablet.

Hypromellose acetate succinate (HPMCAS), the enteric polymer, is essentially insoluble in medium under pH 5 due to the presence of a relatively hydrophobic methyl and acetate group. HPMCAS is usually employed as an enteric coating material for sustained release formulations and applied with a solid dispersion technology [16]. There are some studies in which HPMCAS has been applied to ER matrix tablets [17,18]. However, these studies have not focused on robust dissolution properties in the GI tract of humans.

In this study, HPMCAS and HPC (a hydrophilic polymer) were selected as ER polymers for an ER matrix tablet. ER matrix tablets with a combination of HPMCAS and HPC were prepared (HPMCAS/HPC ER matrix tablet), and the characterization of dissolution properties in several test conditions was evaluated, including an estimation indicating robust dissolution properties and dose-dumping accounting for the variability of pH, mechanical stress in the GI tract, and alcohol-induced effect. Moreover, *in vivo* performance after oral administration of the HPMCAS/HPC ER matrix tablets to humans was simulated by GastroPlus based on dissolution profiles using the USP apparatus 3.

2. Materials and methods

2.1. Materials

Oxycodone hydrochloride, a water soluble drug, was obtained from Daiichi Sankyo Propharma Co., Ltd. (Japan). Hydroxypropylcellulose (HPC-H; fine particle grade, 1000 mPas to 4000 mPas, HPC-SL; 150 mPas to 400 mPas) was purchased from Nippon Soda Co., Ltd. (Japan). Hypromellose acetate succinate (Shin-Etsu AQOAT; LF) was purchased from Shin-Etsu Chemical Co., Ltd. (Japan). D-Mannitol was purchased from Merck Millipore Corporation (Germany). Magnesium stearate (Hyqual, vegetable source) was purchased from Mallinckrodt Pharmaceuticals (USA). All other chemicals and solvents were of reagent grade. The reference product, OxyContin, was purchased from Japanese market purchasing (Shionogi & Co., Ltd., Japan).

2.2. Methods

2.2.1. Preparation of the ER matrix tablets

ER matrix tablets (Rp.1 to Rp. 7 in Table 1) were manufactured as follows. The respective powders were mixed thoroughly with a pestle and mortar. Then the mixtures were weighed and compressed using a single-punch tableting machine (hydraulic pump, Riken power model P-1B, Riken Seiki Co. Ltd., Japan) equipped with a punch and die (diameter of 6 or 7 mm) and operated at a compression force of 1 kN.

2.2.2. In vitro dissolution test (USP apparatus 2)

In vitro dissolution studies were carried out using the USP apparatus 2 (paddle method, NTR-6100A, Toyama Sangyo Co., Ltd.,

Table 1 – Components and compositions for ER matrix tablets.

Components	Compositions (%/tablet)						
	Rp. 1	Rp. 2	Rp. 3	Rp. 4	Rp. 5	Rp. 6	Rp. 7
Oxycodone HCl	8	8	8	8	8	11	5
HPMCAS-LF	30	–	30	43	26	26	26
HPC-H	–	30	30	20	37	37	37
HPC-SL	3	3	3	3	3	3	3
D-mannitol	58	58	28	25	25	22	28
Mg stearate	1	1	1	1	1	1	1
Total (mg)	150	150	150	150	150	100	200