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Research paper

Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations

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ABSTRACT

Taste-masking granules were prepared by coating granules with a taste-masking layer prepared by combining the water-insoluble and -soluble polymers, ethylcellulose and hypromellose, respectively. These granules showed an immediate drug release property after a suitable lag time. We confirmed that the dissolution behavior depended on the polymer ratio in the taste-masking layer. The result showed that the dissolution lag time and rate of the taste-masking granules were shortened and enhanced, respectively by increasing the hypromellose content. Films with the same polymer ratio as the taste-masking layer were prepared, and their physical properties were measured to evaluate the relationship between the dissolution behavior and the film properties. The tensile strength of the films decreased with an increasing concentration of hypromellose. Furthermore, there was a relationship between the tensile strength of the films and dissolution rate of the taste-masking granules. The lag time was significantly shortened when the hypromellose blending ratio exceeded 20%, and this change was suggested to be associated with the water permeability of the film. These results indicate that the tensile strength and water permeability of the films were influenced by the polymer ratio, which also influenced the dissolution behavior of the taste-masking granule.

1. Introduction

The orally disintegrating tablets (ODTs) are in the class of solid dosage forms along with tablets and capsules. It has the benefit of being easy to swallow because it disintegrates instantaneously in the presence of small amounts of saliva in the mouth. Therefore, it is a convenient dosage form for people with poor swallowing ability including children and the elderly. In designing ODTs that contain unpleasant tasting drugs, the taste-masking technique is necessary to improve the drug palatability, and thereby, encourage medication compliance. Recently, various solutions have been developed in the pharmaceutical field in response to the need for taste-masking. For example, taste-masking has been achieved using ingredients such as flavors, sweeteners, and amino acids, as well as other methods such as polymer coating, conventional granulation, desalination, salting-out system, and using ion-exchange resins [1–5].

Although the use of polymers for coating drugs or granules is a useful technique, this process may reduce the drug release, which raises concerns about the possible reduction of drug bioavailability. In addition, the suppression of drug release in the buccal cavity accompanied by immediate drug release in the gastrointestinal tract is highly desirable. It has been reported that the coated fine granules system using an ethylcellulose (EC)/hypromellose (HPMC) membrane allows the achievement of both taste-masking and immediate release from granules by adjusting the ratio of EC and HPMC [6].

Therefore, the purpose of this study was to elucidate the drug release mechanism from taste masking granules (TMGs) coated with an EC/HPMC film. We evaluated the relationship between the tensile strength of the EC/HPMC film and drug dissolution rate of the coated granules. In addition, we considered the influence of the water permeability of the EC/HPMC film on the drug dissolution lag time of the coated granules. Finally, we determined the optimal ratio of EC/HPMC polymer combinations for lafutidine TMGs to

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obtain an immediate drug release property after a suitable lag time.

2. Materials and methods

Lafutidine was obtained from Central Glass Co., Ltd., Japan. Lactose monohydrate (FlowLac 90) was purchased from Meggle, Japan. Hydroxypropyl cellulose (HPC-SSL) was purchased from Nippon Soda Co., Ltd., Japan. Low-substituted hydroxypropyl cellulose (L-HPC LH-31 and LH-21) and HPMC (TC-5E) were purchased from Shin-Etsu Chemical Co., Ltd., Japan. Talc (PKP-81) was purchased from Fuji Talc Industrial Co., Ltd., Japan. EC (Ethocel Std 7 premium) was purchased from Colorcon., Japan. Titanium oxide (TiO_2, NA65) was purchased from Toho Titanium Co., Ltd., Japan. D-mannitol (Mannit Q) was purchased from Mitsubishi Shoji Foodtech Co., Ltd., Japan. Sodium stearyl fumarate (Pruv) was purchased from Kimura Sangyo Co., Ltd., Japan.

2.1. Preparation of TMGs

The schematic representation of the TMG structure is illustrated in Fig. 1 and the granules were prepared according to formulations shown in Table 1 using a previously reported method [7]. First, the drug layer was coated onto the core particles by side spraying in a fluidized bed granulator (MP-01, Powrex, Japan). Next, the separating layer was coated onto the drug layered granules, and then a small amount of talc was added on the separating layer to serve as an antistatic. Finally, the taste-masking layers (EC/HPMC at ratios of 100/0, 90/10, 80/20, 63/33, and 50/50 wt %) were prepared and coated onto different batches of the granules.

2.2. Scanning electron microscopy

The shape and surface morphology of the TMGs were examined using a scanning electron microscope (VE-7800, Keyence, Japan).

2.3. Preparation of ODTs containing TMGs

Each TMG preparation (Table 1) was mixed with the specified excipients according to the formulations shown in Table 2. Then, the mixture was compressed using a hand operated hydraulic pump (B-16B, Riken Seiki Co., Ltd., Japan) to obtain the ODTs (diameter, 8 mm; weight, 220.5 mg).

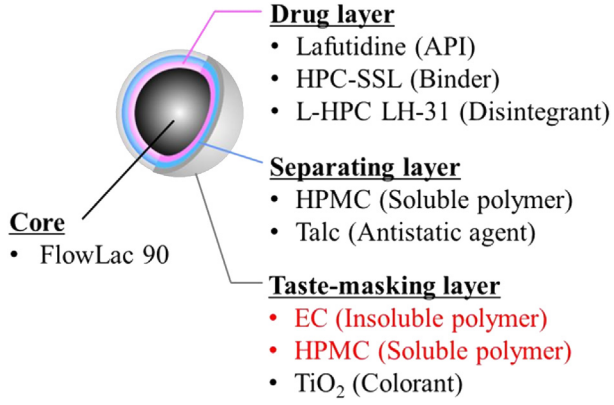

Fig. 1. Schematic representation of taste-masking granule structure. API, active pharmaceutical ingredient; HPC-SSL, hydroxypropyl cellulose; L-HPC LH-31, low-substituted hydroxypropyl cellulose; HPMC, hypromellose; EC, ethylcellulose; TiO_2, titanium oxide.

Table 1
Formulations of taste-masking granules (mg).

ID name	$TMG_{100/0}$	$TMG_{90/10}$	$TMG_{80/20}$	$TMG_{67/33}$	$TMG_{50/50}$
Core					
FlowLac 90	10.0	10.0	10.0	10.0	10.0
Drug layer					
Lafutidine	10.0	10.0	10.0	10.0	10.0
HPC-SSL	10.0	10.0	10.0	10.0	10.0
L-HPC LH-31	4.0	4.0	4.0	4.0	4.0
Separating layer					
HPMC	3.4	3.4	3.4	3.4	3.4
Talc	3.8	3.8	3.8	3.8	3.8
Taste-masking layer					
EC	7.2	6.5	5.8	4.8	3.6
HPMC	–	0.7	1.4	2.4	3.6
TiO_2	3.1	3.1	3.1	3.1	3.1
Total	51.5	51.5	51.5	51.5	51.5

HPC-SSL, hydroxypropyl cellulose; L-HPC LH-31, low-substituted hydroxypropyl cellulose; HPMC, hypromellose; EC, ethylcellulose; TiO_2, titanium oxide.

Table 2
Formulation of orally disintegrating tablets.

	mg/tablet
TMG	51.5
D-mannitol	160
L-HPC LH-21	8
Sodium stearyl fumarate	1
Total	220.5

TMGs, taste-masking granules; L-HPC-LH-31, low-substituted hydroxypropyl cellulose.

2.4. In vitro dissolution study

The dissolution properties of lafutidine from the ODTs were evaluated using a dissolution tester (NTR-6200ACT, Toyama Sangyo Co., Ltd.). The study was conducted in 900 mL of Japanese Pharmacopoeia 1st fluid (JP1) or 2nd fluid (JP2) at 37 ± 0.5 °C with a paddle speed of 50 rpm. Lafutidine was detected using an ultraviolet method (271 nm).

2.5. Preparation of EC/HPMC films

The EC/HPMC films were prepared using the solvent cast method. Briefly, the polymer solution was prepared according to formulations shown in Table 3. EC and HPMC were dissolved in an ethanol-water solvent mixture, stirred overnight, and then the polymer solution was cast on a Teflon plate. The films were allowed to coalesce at 50 °C for 12 h, peeled off using a knife, and then the films with a width and length of 10 and 50 mm, respectively were cut again with a sharp knife to avoid jagged edges. The thickness of the films was measured using a micrometer, and resulting film thickness was 140–200 μm.

Table 3
Formulations of polymer solution for ethylcellulose/hypromellose films.

	EC/HPMC ratio (wt %)				
	100/0	90/10	80/20	67/33	50/50
EC	20	18	16	13.4	10
HPMC	–	2	4	6.6	10
Ethanol	64	64	64	64	64
Water	16	16	16	16	16