Formulation Study for Lansoprazole Fast-disintegrating Tablet. II. Effect of Triethyl Citrate on the Quality of the Products

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The purpose of this study was to develop enteric-coated microgranules for the lansoprazole fast-disintegrating tablet (LFDT), which is a rapidly disintegrating tablet containing enteric-coated microgranules. In our previous study, it was clarified that sufficient flexibility of the enteric layer was achieved by the optimized combined ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion and adding the optimized concentration of triethyl citrate to reduce the damage during the compression process. However, since triethyl citrate has an unpleasant bitter taste and is especially incompatible with lansoprazole, it adversely affects the taste and stability of lansoprazole in the enteric-coated microgranules. The enteric layer containing macrogol 6000 was proven useful to improve the unpleasant bitter taste and stability of lansoprazole, because macrogol 6000 does not have an unpleasant bitter taste and is more compatible than triethyl citerate. By covering the inner (first enteric layer) and outer side (third enteric layer) of the enteric layer containing triethyl citrate (second enteric layer) with the enteric layer containing macrogol 6000, we resolved the stability problem of lansoprazole and the unpleasant bitter taste. Finally, we developed enteric-coated microgranules comprising seven layers: 1) core, 2) active compound layer, 3) intermediate layer, 4) first enteric layer, 5) second enteric layer, 6) third enteric layer, and 7) over coating layer. The enteric-coated microgranules have the multiple functions of reducing the damage to the enteric layer during the compression process, improving the stability of lansoprazole, and masking the unpleasant bitter taste.

Key words lansoprazole; triethyl citrate; stability; taste masking

The lansoprazole fast-disintegrating tablet (LFDT) is a new formulation developed as a rapidly disintegrating tablet containing enteric-coated microgranules. Three issues were considered in the development of LFDT. The first issue is damage to the enteric layer during the compression process, because the enteric-coated microgranules are compressed with a tablet press. In our previous study,[1] it was clarified that sufficient flexibility of the enteric layer was achieved by the optimized combined ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion and adding the optimized concentration of triethyl citrate to reduce the damage during the compression process. The second issue is the taste of LFDT. Since patients take LFDT after disintegration in the mouth, it was thought important to formulate LFDT with a pleasant taste. The third issue is the stability of lansoprazole in LFDT, because lansoprazole is incompatible with many excipients.

The purpose of this study was to develop enteric-coated microgranules with an improved taste and the stabilization of lansoprazole. Since triethyl citrate has an unpleasant bitter taste and is an oily liquid,[2] it was anticipated that it would affect the taste of the enteric-coated microgranules and the stability of lansoprazole. Tabata *et al.*[3] reported that the degradation content of lansoprazole should be proportional to the product of the degradation rate constant and the total solubility of lansoprazole and suggested that lansoprazole in enteric dosage form would be unstable when it coexisted with a liquid and would be easy to dissolve. We studied the effects of triethyl citrate on the unpleasant bitter taste and stability of lansoprazole in enteric-coated microgranules and also attempted to formulate enteric-coated microgranules by masking the unpleasant bitter taste and improving the stability of lansoprazole.

Experimental

Materials Lansoprazole was synthesized at Takeda Chemical Industries, Ltd. Commercial lansoprazole capsules were obtained in-house at Takeda Chemical Industries, Ltd.

Lactose monohydrate-microcrystalline cellulose spheres (Nonpareil 105T, mean particle size 150—180 μm) and low-substituted hydroxypropyl cellulose (LH-33, hydroxypropoxy groups 5.0—6.9%) were kindly supplied by Freund Industrial Co., Ltd., and Shin-Etsu Chemical Co., Ltd., respectively. Methacrylic acid copolymer dispersion (Eudragit® L30D-55) and ethyl acrylate–methyl methacrylate copolymer dispersion (Eudragit® NE30D) were purchased from Rölm GmbH. Low-substituted hydroxypropyl cellulose (LH-32, hydroxypropoxy groups 7.0—9.9%) and hydroxypropyl methylcellulose 2910 (TC-5 EW) were purchased from Shin-Etsu Chemical Co., Ltd. Mannitol and polysorbate 80 were purchased from Merck Japan Ltd. Magnesium carbonate (Tomita Pharmaceutical Co., Ltd.), hydroxypropyl cellulose (HPC-SSL, Nippon Soda Co., Ltd.), talc (Matsumura Industrial Co., Ltd.), titanium dioxide (Freund Industrial Co., Ltd.), citric acid (A. D. M. Faryast, Ltd.), glyceryl monostearate (P-100, Riken Vitamin Co., Ltd.), macrogol 6000 (Sanyo Chemical Industrial, Ltd.), triethyl citrate (Citroflex 2, Morimura Bros., Inc.), microcrystalline cellulose (Ceolus KG-801, Asahi Chemical Industry Co., Ltd.), crospovidone (Polyplasdone XL-10, ISP Japan Ltd.), and magnesium stearate (Taihei Chemical Industrial Co., Ltd.) were purchased. Yellow ferric oxide (Anstead International Co., Ltd.) and red ferric oxide (BASF Japan Ltd.) were used as the pigment. Asparteme (Ajinomoto Co., Ltd.) was used as the sweetening agent. Strawberry durarome (Firmenich) was used as the flavoring agent. All other excipients used in the dosage forms are specified in the Japanese Pharmacopoeia (JP) and Japanese Pharmaceutical Excipients.

Preparation of LFDTs LFDTs consist of enteric-coated microgranules containing lansoprazole and inactive granules, as shown in Chart 1. The mean particle size of the enteric-coated microgranules was approximately 300 μm and they were comprised of four, five, or seven layers, as shown in Charts 1 and 2.

Coating of Active Compound Layer and Intermediate Layer Table 1 presents the formulation in the preparation of lansoprazole-coated microgranules. An active compound suspension consisting of lansoprazole, mag-

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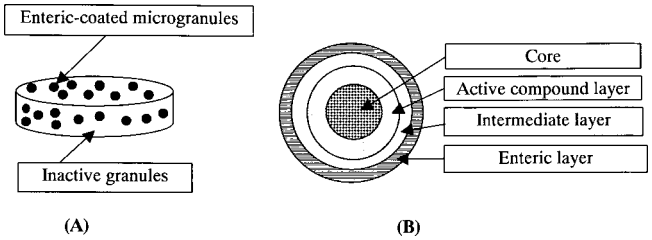

Chart 1. Structure of Lansoprazole Fast-Disintegrating Tablets (A) and Cross-Section of Enteric-Coated Microgranules (B)

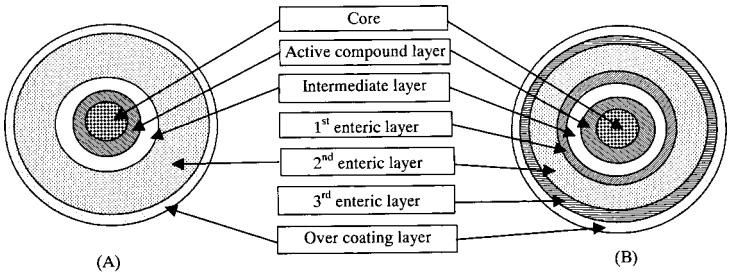

Chart 2. Cross-Section of Enteric-Coated Microgranules

(A) Enteric-coated microgranules comprised of five layers; (B) enteric-coated microgranules comprised of seven layers.

Table 1. Formulation of Lansoprazole-Coated Microgranules

Core	Lactose monohydrate-microcrystalline cellulose spheres	30.0 mg
Active compound layer	Lansoprazole	30.0 mg
	Magnesium carbonate	10.0 mg
	Low-substituted hydroxypropyl cellulose (LH-32)	5.0 mg
	Hydroxypropyl cellulose	10.0 mg
	Purified water[a)]	128 μl
Intermediate layer	Hydroxypropyl methycellulose 2910	9.5 mg
	Other[b)]	0.5 mg
	Purified water[a)]	40 μl
	Total	95.0 mg

a) Removed during processing. *b*) Low-substituted hydroxypropyl cellulose (LH-32) and/or talc and /or titanium dioxide and/or mannitol.

Table 2. Operating Conditions for Enteric-Coated Microgranules

	Active compound layer	Intermediate layer	Enteric layer	Over coating layer
Total charge amount (kg)	2.1—2.6	2.8—3.3	2.6—3.6	2.7—3.8
Inlet air volume (m^3/min)	1.0	1.5	1.5	1.5
Inlet air temperature (°C)	65—80	70—80	65—80	65—85
Product temperature (°C)	*ca.* 30	*ca.* 40	*ca.* 40	*ca.* 35
Atomizing air volume (Nl/min)	80	100	100	100
Spray rate (g/min)	*ca.* 20	*ca.* 20	*ca.* 20	*ca.* 20
Rotor speed (rpm)	500	550	600	600

nesium carbonate, low-substituted hydroxypropyl cellulose (LH-32), hydroxypropyl cellulose, and purified water was prepared by stirring. An intermediate suspension consisting of hydroxypropyl methycellulose 2910, other ingredients, and purified water was prepared by stirring. Lactose monohydrate-microcrystalline cellulose spheres were coated consecutively by spraying the active compound suspension and the intermediate suspension in a rotating fluidized-bed granulator (Multiplex MP-10, Powrex Co., Ltd., Japan). Table 2 lists the operating conditions for coating. The above granules were dried in the rotating fluidized-bed granulator.

Coating of the Enteric Layer Tables 3 and 4 present the formulations in the preparation of the enteric layer. A glyceryl monostearate emulsion consisting of glyceryl monostearate, polysorbate 80, pigment, and purified water was prepared by homogeneous dispersion with a dispersing machine. An enteric coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate–methyl methacrylate copolymer dispersion, glyceryl monostearate emulsion, macrogol 6000, citric acid, and purified water was prepared by stirring. An enteric coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate–methyl methacrylate copolymer dispersion, glyceryl monostearate emulsion, triethyl citrate, citric acid, and purified water was prepared by stirring. An over coating solution consisting of mannitol and purified water was prepared by stirring.

Lansoprazole-coated microgranules were coated consecutively by spraying part of the first enteric coating suspension, the second enteric coating suspension, the remainder of the first enteric coating suspension, and the over coating solution in the rotating fluidized-bed granulator. Table 2 lists the operating conditions for coating. The above granules were then dried in the rotating fluidized-bed granulator.

Preparation of LFDTs The enteric-coated microgranules, mannitol, low-substituted hydroxypropyl cellulose (LH-33), microcrystalline cellulose, crospovidone, other ingredients, and magnesium stearate were mixed at the weight ratio shown in Table 5. The mixed granules were compressed with a rotary tablet press (Correct 12HUK, Kikusui Seisakusho, Ltd., Japan).

Table 3. Formulations of Enteric-Coated Microgranules

Formulation no.	1	2	3
Lansoprazole-coated microgranules			
Core	30.0 mg	30.0 mg	30.0 mg
Active compound layer[a)]	55.0 mg	55.0 mg	55.0 mg
Intermediate layer[b)]	20.0 mg	20.0 mg	25.0 mg
Enteric layer containing macrogol 6000			
Methacrylic acid copolymer dispersion[c)]	—	67.4 mg	15.26 mg
Ethyl acrylate–methyl methacrylate copolymer dispersion[c)]	—	7.5 mg	1.7 mg
Macrogol 6000	—	15.0 mg	1.7 mg
Glyceryl monostearate	—	3.2 mg	1.0 mg
Polysorbate 80	—	1.3 mg	0.3 mg
Talc	—	5.3 mg	—
Citric acid	—	—	0.02 mg
Pigment	—	5.3 mg	0.02 mg
Purified water[d)]	—	140.2 μl	70 μl
Enteric layer containing triethyl citrate			
Methacrylic acid copolymer dispersion[c)]	69.5 mg	—	84.0 mg
Ethyl acrylate–methyl methacrylate copolymer dispersion[c)]	7.7 mg	—	9.33 mg
Triethyl citrate	15.5 mg	—	18.7 mg
Glyceryl monostearate	5.2 mg		6.0 mg
Polysorbate 80	1.7 mg	—	1.8 mg
Citric acid	—	—	0.05 mg
Pigment	5.4 mg	—	0.12 mg
Purified water[d)]	134.9 μl	—	142 μl
Enteric layer containing macrogol 6000			
Methacrylic acid copolymer dispersion[c)]	—	—	7.63 mg
Ethyl acrylate–methyl methacrylate copolymer dispersion[c)]	—	—	0.85 mg
Macrogol 6000	—	—	0.85 mg
Glyceryl monostearate	—	—	0.50 mg
Polysorbate 80	—	—	0.15 mg
Citric acid	—	—	0.01 mg
Pigment	—	—	0.01 mg
Purified water[d)]	—	—	35 μl
Over-coating layer			
Mannitol	—	—	10.0 mg
Purified water[d)]	—	—	60 μl
Total	210.0 mg	210.0 mg	270.0 mg

a) Composition of the active compound layer is the same as shown in Table 1. *b*) Composition of the intermediate layer is the same as shown in Table 1. *c*) Dry lacquer substance. *d*) Removed during processing.

Table 4. Formulations of Enteric-Coated Microgranules (mg)

Amount of the enteric layer containing macrogol 6000	0	15	20	30
Core	30.0	30.0	30.0	30.0
Active compound layer[a)]	60.0	60.0	60.0	60.0
Intermediate layer[b)]	30.0	30.0	30.0	30.0
Enteric layer containing macrogol 6000[c)]	—	15.0	20.0	30.0
Enteric layer containing triethyl citrate[d)]	100.0	100.0	90.0	70.0
Enteric layer containing macrogol 6000[c)]	—	15.0	20.0	30.0
Over coating layer	10.0	10.0	10.0	10.0
Total	230.0	260.0	260.0	260.0

a) Composition of the active compound layer is the same as shown in Table 1. *b*) Composition of the intermediate layer is the same as shown in Table 1. *c*) Composition of the enteric layer is the same proportion of the enteric layer containing macrogol 6000 as shown in Table 3 (formulation no. 3). *d*) Composition of the enteric layer is the same proportion of the enteric layer containing triethyl citrate as shown in Table 3 (formulation no. 3).

Tablets 530 mg, 560 mg, or 570 mg in weight and 13 mm in diameter were prepared at 30 rpm compression speed and 14.7 kN/cm^2 compression force.

Sensory Evaluation of the Bitter Taste A sensory test of enteric-coated microgranules and LFDTs was carried out in 3 volunteers. After the mouth was rinsed with water, the enteric-coated microgranules (equivalent to lansoprazole 30 mg) or LFDT was held in the mouth for about 60 s and then spat out, and the mouth was rinsed again. The bitterness level was then recorded. A numerical scale was used with the following values: 0, tasteless; 1, very slight; 2, slight; 3, moderate; and 4, strong.

Dissolution Rate of Methacrylic Acid Copolymer Glass beads 1.0 mm in diameter were coated with the enteric layer, for which the formula is shown in Table 6, and dried using fluid-bed granulator (Mutiplex MP-10, Powrex Co., Ltd.).

The dissolution rates of methacrylic acid copolymer dispersion were tested according to the elution test method of JP Article 66. A dissolution apparatus (paddle method) was used. The dissolution medium consisted of 500 ml of 1/15 M phosphate buffer (KH_2PO_4–Na_2HPO_4, pH 5.7, pH 6.1, and pH 6.8). The revolving rate was 50 rpm and temperature was set to 37 °C. The glass beads (4325 mg) coated with the enteric layer (W_{T1}) equivalent to 300 mg of methacrylic acid copolymer were accurately weighed, transferred

Table 5. Formulations of LFDT (mg)

Enteric-coated microgranules	230.0 or 260.0 or 270.0
Mannitol	204.0
Low-substituted hydroxypropyl cellulose (LH-33)	30.0
Microcrystalline cellulose	30.0
Crospovidone	15.0
Citric acid	3.0
Aspartame	9.0
Flavor	3.0
Magnesium stearate	6.0
Total	530.0 or 560.0 or 570.0

Table 6. Formulations of Enteric Layer containing Macrogol 6000

Glass beads	100.0 mg
Methacrylic acid copolymer dispersion[a)]	7.63 mg
Ethyl acrylate–methyl methacrylate copolymer dispersion[a)]	0.85 mg
Macrogol 6000	0.85 mg
Glyceryl monostearate	0.50 mg
Polysorbate 80	0.15 mg
Citric acid	0.01 mg
Pigment	0.01 mg
Purified water[b)]	35 μl
Total	110.0 mg

a) Dry lacquer substance. *b*) Removed during processing.

to a vessel, and titrated with 0.5 M sodium hydroxide to maintain the pH of the medium, while monitoring the pH using a pH meter. After 1, 2, and 3 min, the 0.5 M sodium hydroxide consumed was weighed on a balance (W_{T2}). The measurement was repeated 3 times for each pH level.

Separately, the glass beads (4325 mg) coated with the enteric layer (W_{S1}) equivalent to 300 mg of methacrylic acid copolymer were accurately weighed and transferred to a beaker. Methacrylic acid copolymer was dissolved completely in 500 ml of each medium using a magnetic stirrer and then the 0.5 M sodium hydroxide consumed was weighed on a balance (W_{S2}) to maintain the pH of the medium. The amount of methacrylic acid copolymer dissolved was calculated at each time with the following formula.

$$\text{dissolution amount (mg)} = 300 \times (W_{T2} \times 4325/W_{T1})/(W_{S2} \times 4325/W_{S1})$$

Saliva pH Measurement Saliva pH measurement was carried out in 8 volunteers. After the mouth was rinsed with water, one tablet was held in the mouth for 1 min to disintegrate the tablet without chewing. The saliva pH after 1 min was measured using a pH meter (Twin pH meter, Type B-211, Horiba Seisakusho, Japan).

Compatibility Study Lansoprazole was mixed with each excipient at an appropriate ratio.[3)] Each mixture was stored in a closed glass bottle at 60 °C for 1 week and in an open glass bottle at 40 °C/75% relative humidity (RH) for 1 week. Lansoprazole was also stored alone as a reference. The lansoprazole was then assayed using HPLC.[3)]

Stress Stability of Lansoprazole in Enteric-Coated Microgranules Enteric-coated microgranules were stored in a closed glass bottle at 60 °C for 2 weeks and 4 weeks. The lansoprazole was then assayed using HPLC.[3)]

Accelerated Stability of Lansoprazole in LFDTs LFDTs and lansoprazole capsules were stored in an aluminum/aluminum blister at 40 °C/75% RH for 2 months, 4 months, and 6 months. The lansoprazole was then assayed using HPLC.[3)]

Dissolution Testing Dissolution tests were performed in accordance with USP 24 Dissolution ⟨711⟩ and Drug Release ⟨724⟩ using apparatus 2 (paddle). The paddle was driven at 75 rpm. The test comprises the following two stages.

Acid Stage: Five hundred milliliters of 0.1 N HCl was used as the dissolution medium. The dissolution percentage after 60 min was measured. The amount of lansoprazole dissolved in the dissolution medium was determined by spectrophotometry (wavelength: 306 nm) after filtration through a membrane filter (0.45 μm, Acrodisc LC : PVDF, Gelman, P/N 44080).

Buffer Stage: Immediately after the test medium was withdrawn from the acid stage, 425 ml of the buffer concentrate (pH 11.4) was added and 900 ml of phosphate buffer containing 5 mM sodium dodecyl sulfate (pH 6.75—6.85) was obtained. The medium samples were collected at 15, 30, 45, and 60 min. The amount of lansoprazole dissolved in the dissolution medium was determined by spectrophotometry (wavelength: 286 nm) after filtration through a membrane filter (0.45 μm, Acrodisc LC : PVDF, Gelman, P/N 4408).

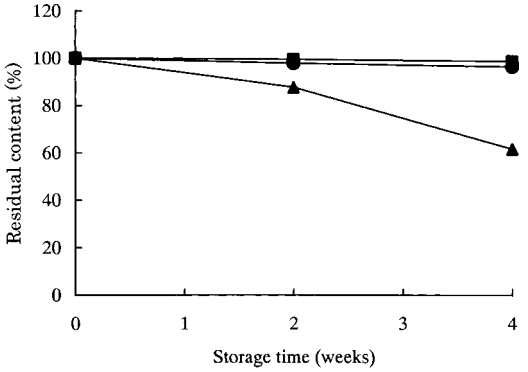

Fig. 1. Comparison of Stress Stability between Enteric-Coated Microgranules for LFDT and Lansoprazole Capsules Stored at 60 °C in a Closed Bottle

▲, enteric-coated microgranules containing triethyl citrate; ■, lansoprazole capsules; ●, enteric-coated microgranules containing macrogol 6000.

Results and Discussion

Effect of Triethyl Citrate on the Quality of Enteric-Coated Microgranules In our previous study,[1)] four different formulations of enteric-coated microgranules containing increased concentrations of triethyl citrate were prepared to investigate the effects of the triethyl citrate concentration on the damage to the enteric layer during the compression process. When we evaluated the unpleasant bitter taste of these enteric-coated microgranules in a sensory evaluation, it was found that the unpleasant bitter taste tended to increase with the increase in the triethyl citrate concentration.

Stress stability testing with the enteric-coated microgranules containing triethyl citrate using formulation no. 1 in Table 2 was carried out. Lansoprazole in enteric-coated microgranules was markedly less stable than that in current lansoprazole capsules, as shown in Fig. 1. To clarify the effects of triethyl citrate on the stability of lansoprazole in enteric-coated microgranules, the compatibility of lansoprazole with a number of excipients used in these formulations was investigated. Incompatibility was noted for four excipients, triethyl citrate, macrogol 6000, polysorbate 80, and glyceryl monostearate, which caused significant degradation at high temperature (60 °C), as shown in Table 7. Lansoprazole is remarkably incompatible with triethyl citrate. These data confirm that triethyl citrate induces the unpleasant bitter taste and poor stability of lansoprazole in enteric-coated microgranules.

Replacement of Triethyl Citrate with Macrogol 6000 To improve the unpleasant bitter taste and stability of lansoprazole in enteric-coated microgranules, triethyl citrate should be replaced with a more appropriate plasticizer, which does not have an unpleasant bitter taste and is compatible with lansoprazole. From the results of the compatibility study shown in Table 7, it was recognized that lansoprazole is comparatively compatible with solid excipients, but is incompatible with the excipients with low melting points (macrogol 6000 and glyceryl monostearate) and liquid excipients (triethyl citrate and polysorbate 80). The degradation of

Table 7. Compatibility of Lansoprazole with Some Excipients at 60 °C in a Closed Bottle and 40 °C/75% Relative Humidity in an Open Bottle

Excipient	Ratio	Assay of lansoprazole (residual content %)	
	Lansoprazole/excipient	60 °C 1 week	40 °C/75%RH 1 week
Lansoprazole alone		100.6	100.3
Lactose monohydrate-microcrystalline cellulose spheres	5/1	104.9	101.1
Magnesium carbonate	5/1	100.1	99.3
Low-substituted hydroxypropyl cellulose (LH-32)	5/1	100.1	98.2
Hydroxypropyl cellulose	5/1	100.6	98.2
Hydroxypropyl methylcellulose 2910	5/1	100.6	98.9
Talc	5/1	100.3	99.6
Glyceryl monostearate	5/1	71.5	100.2
Polysorbate 80	5/1	61.9	98.5
Triethyl citrate	5/1	0.0	98.8
Macrogol 6000	5/1	39.5	99.7

lansoprazole should be enhanced by dissolving in liquid excipients and melted excipients because the degradation content of lansoprazole should be proportional to the product of the degradation rate constant and the total solubility of lansoprazole. Since plasticizers such as triacetin, tributyl citrate, *etc.* have an unpleasant bitter taste and are oily liquids like triethyl citrate, they are also inappropriate as plasticizers in this formulation.

Macrogol 6000, which is used as the plasticizer in the enteric layer in current lansoprazole capsules, has a comparatively low melting point, but is solid at ambient temperatures. It is incompatible with lansoprazole at high temperature (60 °C), but the lansoprazole in current capsules is stable, as shown in Fig. 1. Therefore we selected macrogol 6000 as the plasticizer for triethyl citrate in this study.

Enteric-coated microgranules containing macrogol 6000, which was the same as the concentration of the plasticizer, were prepared as shown in Table 2 (formulation no. 2) and stress stability testing was carried out. With enteric-coated microgranules containing macrogol 6000 as the plasticizer, lansoprazole was stable, as shown in Fig. 1. We also confirmed that enteric-coated microgranules containing macrogol 6000 did not have an unpleasant bitter taste. However, it was found that enteric-coated microgranules containing macrogol 6000 with a 20% concentration of the gross solid weight of methacrylic acid copolymer dispersion and ethyl acrylate–methyl methacrylate copolymer dispersion are difficult to prepare because of the occurrence of agglomerates of enteric-coated microgranules during the enteric coating process. It was thought that the occurrence of the agglomerates was due to the lower melting point. When macrogol 6000 (melting point, 60—63 °C) and glyceryl monostearate (melting point, 55—60 °C), which was used as an agglomerating agent in the enteric layer, coexist in the enteric layer, a lower melting point should occur and the cohesiveness between enteric-coated microgranules should be enhanced. Therefore enteric-coated microgranules could be prepared by adding talc as an antiagglomerating agent to reduce the cohesion force. Macrogol 6000 is useful to improve the unpleasant bitter taste and stability of lansoprazole in enteric-coated microgranules, but triethyl citrate could not be replaced with macrogol 6000 because the flexibility of the enteric layer containing macrogol 6000 is reduced by adding talc to decrease the damage to the enteric layer during the compression process.[1)]

Effects of the Enteric Layer Containing Macrogol 6000 Various masking techniques such as the addition of sweeteners and flavorings, coating with water-soluble polymers, water-insoluble polymers,[4)] or pH-dependent water-soluble polymers,[5,6)] filling in capsules, complexing with cyclodextrins,[7)] adsorption on ion-exchange resin,[8)] and microencapsulation[9)] have been attempted. Masking the properties of triethyl citrate in the enteric layer was thought to improve the unpleasant bitter taste and stability of lansoprazole. We thus coated the inner and outer side of the enteric layer containing triethyl citrate with another layer. Chart 2 shows the structure of enteric-coated microgranules comprised of seven layers: 1) core, 2) active compound layer, 3) intermediate layer, 4) first enteric layer (improving the stability of lansoprazole), 5) second enteric layer (the enteric layer containing triethyl citrate), 6) third enteric layer (masking layer), and 7) over coating layer. Mannitol was used as the over coating layer to prevent agglomerates of the enteric-coated microgranules during the drying process after the enteric coating process.

The enteric layer comprised of methacrylic acid copolymer dispersion and macrogol 6000 was selected because macrogol 6000 does not have an unpleasant bitter taste and enteric-coated microgranules comprised of methacrylic acid copolymer dispersion and macrogol 6000 were stable, as shown in Fig. 1. Furthermore, the enteric layer containing macrogol 6000 at low concentrations could be coated because the cohesiveness between enteric-coated microgranules during the enteric coating process decreased by adding a low concentration of macrogol 6000.

The amount of the first and third enteric layers should mask the unpleasant bitter taste and improve the stability of lansoprazole. Four representative formulations of enteric-coated microgranules were prepared with different amounts of these enteric layers, as shown in Table 4, and LFDTs were prepared, as shown in Table 5. It was reported that enteric granules with an enteric layer of about 50 μm showed satisfactory acid resistance and dissolution profiles in the buffer stage.[10)] The total amount of the three enteric layers was fixed at 130 mg (thickness of the enteric layers, approximately 50 μm), and the amount of the enteric layer containing triethyl citrate decreased with the increase in the amount of the enteric layer containing macrogol 6000.

Stress stability testing of lansoprazole with enteric-coated microgranules stored in a closed bottle at 60 °C for 2 weeks was carried out and the lansoprazole was assayed. As the

Table 8. Effect of Amount of Enteric Layer Containing Macrogol 6000 on the Stability of Lansoprazole and the Dissolved Percentage of LFDT in the Acid Stage

Amount of the enteric layer containing macrogol 6000	0 mg	15 mg	20 mg	30 mg
Assay of lansoprazole (residual content, %)	94.7	95.9	97.7	98.5
Dissolved percentage of LFDT in the acid stage (%)[a)]	3.4±0.5	3.8±0.7	5.4±0.9	6.5±0.9

a) The data are expressed as mean±S.D. (n=3).

amount of the enteric layer containing macrogol 6000 (the first enteric layer) increased, the stability of lansoprazole improved, as shown in Table 8.

Since the brittle character of methacrylic acid copolymer dispersion was reduced by adding the optimized concentration of triethyl citrate, it was considered that the flexibility of the enteric layers might decrease by coating the enteric layer containing triethyl citrate (the second enteric layer) with enteric layers containing macrogol 6000, for which the efficiency of plasticization is lower than that of triethyl citrate. The dissolved percentage of LFDT in the acid stage increased with the increase in the amount of enteric layers containing macrogol 6000 (the first and third enteric layers). However, enteric-coated microgranules with 30 mg of enteric layers containing macrogol 6000 (the first and third enteric layers) and 100 mg of the enteric layer containing triethyl citrate (the second enteric layer) showed similar flexibility of the enteric layers to that without the first and third enteric layers containing macrogol 6000, as shown in Table 8. It was also confirmed that the unpleasant bitter taste could be masked for 60 s in all enteric layers containing macrogol 6000 (the first enteric layer) in the sensory evaluation for the unpleasant bitter taste.

It was recognized that the total amount of enteric layers containing macrogol 6000 (the first and third enteric layers) should be not more than 30 mg for the flexibility of the enteric layers, but a large amount of the intermediate layer and enteric layer containing macrogol 6000 (the first enteric layer) was desirable for the stability of lansoprazole. Therefore we selected enteric-coated microgranules in which the amount of the masking layer (the third enteric layer) was decreased, as shown in Table 3 (formulation no. 3) and LFDTs were prepared as shown in Table 5.

The accelerated stability tests of LFDTs and lansoprazole capsules were carried out and the lansoprazole was assayed. The stability of lansoprazole in LFDTs was similar to that of lansoprazole capsules, as shown in Fig. 2. The data suggest that methacrylic acid copolymer dispersion and macrogol 6000 were approximate components to prevent contact with triethyl citrate.

Six LFDT lots were prepared to verify the reproducibility of the flexibility of the enteric layers. Since the mean dissolved percentage of LFDT in the acid stage was 3.2±0.5% (mean±S.D., n=6), it was confirmed that the flexibility was reproducible. Furthermore, the dissolution profiles of LFDTs in the buffer stage were comparable with that of current lansoprazole capsules and were also similar to those of traditional lansoprazole capsules, as shown in Fig. 3.

Methacrylic acid copolymer dispersion dissolves at higher than pH 5.5, and the dissolution rate of methacrylic acid copolymer dispersion increases slowly with an increase in pH.[11] Since the saliva is generally pH 5—6 at rest and

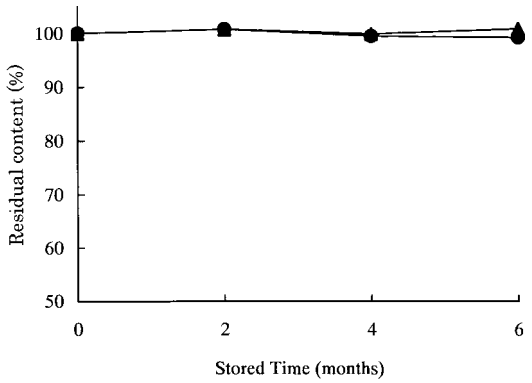

Fig. 2. Comparison of Accelerated Stability of Lansoprazole between LFDT and Lansoprazole Capsules

●, LFDT; ▲ lansoprazole capsules.

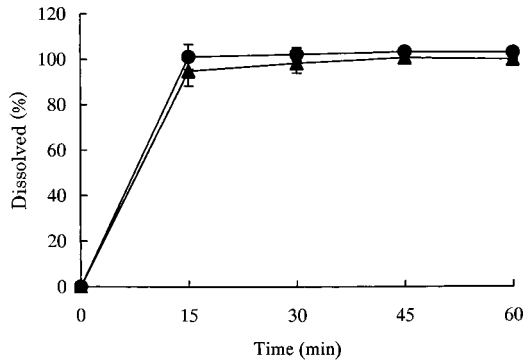

Fig. 3. Comparison of Dissolution Profiles in the Buffer Stage

The data are expressed as mean±S.D. (n=3). ●, LFDT; ▲, lansoprazole capsules.

reaches pH 8 when the secretion rate increases, the dissolution rate of the enteric layer containing macrogol 6000 (the third enteric layer) at saliva pH might affect the masking efficiency. The dissolution rate of methacrylic acid copolymer was evaluated in media with pH higher than 5.5. Methacrylic acid copolymer was not dissolved within 1 min in all media, as shown in Fig. 4. Methacrylic acid copolymer exhibited the same dissolution profiles in media with pH 5.7 and 6.1 and a rapid dissolution profile in the pH 6.8 medium. Since methacrylic acid copolymer does not dissolve rapidly even at pH higher than 5.5, the enteric layer should not dissolve in the mouth in a short time and the masking of the unpleasant bitter taste using methacrylic acid copolymer dispersion is appropriate. We evaluated the saliva pH and bitter taste when LFDT was held in the mouth for 1 min. The mean saliva pH was pH 5.7±0.2 (mean±S.D., n=8). The saliva pH did not become lower than pH 5.5, but the unpleasant bitter taste was masked for 60 s.

Methacrylic acid coplymer dispersion and macrogol 6000

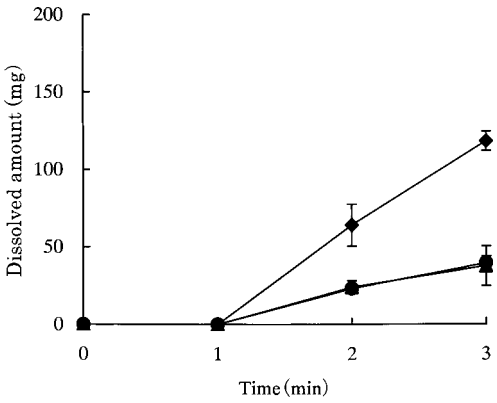

Fig. 4. Effect of the pH of the Buffer Solution on Dissolution Rate of Methacrylic Acid Copolymer

The data are expressed as mean±S.D. (n=3). pH of the medium: ●, pH 5.9; ▲, pH 6.1; ■, pH 6.8.

played an important role in improving the unpleasant bitter taste and the poor stability of lansoprazole. The unpleasant bitter taste was masked by coating with methacrylic acid coplymer and macrogol 6000. Although the plasticization of macrogol 6000 is less efficient than that of triethyl citrate, but sufficient flexibility of the enteric layers was achieved by optimizing the amount of the enteric layer containing macrogol 6000. The stability of lansoprazole was improved by optimizing the amount of the intermediate layer and the enteric layer containing macrogol 6000.

Conclusions

Triethyl citrate plays an important role in the formulation of enteric-coated microgranules to reduce the brittle character of methacrylic acid copolymer dispersion,[1)] but it has an unpleasant bitter taste and is especially incompatible with lansoprazole. It was found that triethyl citrate adversely affects the taste and the stability of lansoprazole. The enteric layer comprised of methacrylic acid copolymer and macrogol 6000 as a plasticizer was proven useful to improve the stability of lansoprazole and the unpleasant bitter taste. By covering the inner (first enteric layer) and the outer side (third enteric layer) of the enteric layer containing triethyl citrate (second enteric layer) with the enteric layer containing macrogol 6000, we improved the stability and taste. Finally, we developed seven-layered enteric-coated microgranules comprised of the: 1) core, 2) active compound layer, 3) intermediate layer, 4) first enteric layer, 5) second enteric layer, 6) third enteric layer, and 7) over coating layer. Enteric-coated microgranules have multiple functions such as the masking the unpleasant bitter taste, providing sufficient flexibility of the enteric layers, and stabilization of lansoprazole.

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References and Notes

1) Shimizu T., Nakano Y., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, **51**, 942—947 (2003).
2) Kibbe A. H. (ed.), "Handbook of Pharmaceutical Excipients," third edition, American Pharmaceutical Association, Washington, DC, USA, 2000.
3) Tabata T., Makino T., Kashihara T., Hirai S., Kitamori N., Toguchi H., *Drug Dev. Ind. Pharm.*, **18**, 1437—1447 (1992).
4) Sugao H., Yamazaki S., Shiozawa H., Yano K., *J. Pharm. Sci.*, **87**, 96—100 (1998).
5) Nakagami H., Keshikawa T., Matsumura M., Tsukamoto H., *Chem. Pharm. Bull.*, **39**, 1837—1842 (1991).
6) Ishikawa T., Watanabe Y., Utoguchi N., Matsumoto M., *Chem. Pharm. Bull.*, **47**, 1451—1454 (1999).
7) Takahashi Y., Tsukuda T., Izumi C., Ikemoto K., Kokubun K., Yagi N., Takeda M., *Chem. Pharm. Bull.*, **36**, 2708—2710 (1998).
8) Friend D. R., *J. Microencapsulation*, **9**, 469—480 (1992).
9) Fu Lu Y. F., Borodkin S., Woodward L., Li P., Diesner C., Hernandez L., Vadnere M., *Pharm. Res.*, **8**, 706—712 (1991).
10) Tabata T., Makino T., Kikuta J., Hirai S., Kitamori N., *Drug Dev. Ind. Pharm.*, **20**, 16621—1672 (1994).
11) "Brochure of Methacrylic Acid Copolymer Dispersion," prepared by Röhm GmbH, Darmstadt, Germany, 1996.