Formulation Study for Lansoprazole Fast-disintegrating Tablet. III. Design of Rapidly Disintegrating Tablets

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Lansoprazole fast-disintegrating tablets (LFDT) are a patient-friendly formulation that rapidly disintegrates in the mouth. LFDT consist of enteric-coated microgranules (mean particle size, approximately 300 μm) and inactive granules. In the design of the inactive granules, mannitol was used as a basic excipient. Microcrystalline cellulose, low-substituted hydroxypropyl cellulose (L-HPC), and crospovidone were used as binders and disintegrants. A new grade of L-HPC (L-HPC-33), with a hydroxypropoxy group content of 5.0—6.9%, was developed and it has no rough texture due to a decrease in water absorption. It was clarified that L-HPC-33 could be useful as a binder and disintegrant in rapidly disintegrating tablets. LFDT contain enteric-coated microgranules in tablet form. The enteric-coated microgranule content in LFDT affect qualities such as tensile strength, disintegration time in the mouth, and dissolution behavior in the acid stage and in the buffer stage of LFDT. The 47.4% content of the enteric-coated microgranules was selected to give sufficient tensile strength (not less than 30 N/cm^2), rapid disintegration time in the mouth (not more than 30 s), and dissolution behavior in the acid stage and buffer stage similar to current lansoprazole capsules. Compression force affected the tensile strength and the disintegration time in the mouth, but did not affect the dissolution behavior in the acid and buffer stages.

Key words rapidly disintegrating tablets; roughness; L-HPC; compression force; dissolution

Tablets that disintegrate rapidly in the mouth are convenient for patients who have difficulty in swallowing conventional oral dosage forms. Although various manufacturing technologies such as tablet molding,[1,2] freeze-drying,[3—7] spray-drying,[8—11] disintegrant addition,[12—16] sublimation,[17] and sugar-based excipients[18] have been studied, rapidly disintegrating tablets that are superior in both pharmaceutical function, for example, sustained-release dosage forms and enteric dosage forms, and in case of swallowing have rarely been reported. Lansoprazole, a substituted benzimidazole, is a highly specific inhibitor of gastric ($H^+ + K^+$)-ATPase.[19,20] Since lansoprazole is unstable under acidic conditions, it is necessary to design enteric dosage forms that can protect against degradation in the stomach. Lansoprazole is marketed as a capsule containing enteric-coated granules, but some patients may find capsules difficult to swallow due to their size. Therefore it has been thought necessary to develop a patient-friendly enteric dosage form that is easy to swallow.

The purpose of this study was to develop a new formulation of lansoprazole, lansoprazole fast-disintegrating tablets (LFDT), which are rapidly disintegrating tablets that are easy to swallow as well as an enteric dosage form, with a simple manufacturing method using a conventional tablet press. LFDT consist of enteric-coated microgranules and inactive granules. In our previous studies,[21,22] we reported the design of multifunctional enteric-coated microgranules with improved oral acceptance, sufficient flexibility of the enteric layers against compression, and improved stability of lansoprazole. In the design of the inactive granules, it was necessary to find a suitable binder with excellent compactibility and a suitable rapid disintegrant in saliva. We formulated the inactive granules using four excipients, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose (L-HPC), and crospovidone. Mannitol was used as the basic excipient because it has a sweet taste and leaves a cooling sensation in the mouth. Microcrystalline cellulose was used as a binder as it has high water absorbency, and tablets containing microcrystalline cellulose are characterized by short disintegration time, high hardness, and low friability. L-HPC was used as a binder and disintegrant because it has different properties as a binder and disintegrant by selecting particle size and substitution level (hydroxypropoxy group content). Crospovidone was used as a disintegrant as it rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gel. However, the rapidly disintegrating tablets comprised of a large amount of water-insoluble excipients may feel rough. We evaluated the effects of hydroxypropoxy group content in L-HPC on the sensation of LFDT and clarified the effects of compression on the properties of LFDT, such as the tensile strength, disintegration time in the mouth, dissolved percentage in the acid stage, and dissolution profiles in the buffer stage.

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 L-HPC (hydroxypropoxy groups: L-HPC-33, 5.0—6.9%; L-HPC-30, 13.0—16.0%) 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. L-HPC (hydroxypropoxy groups: L-HPC-32, 7.0—9.9%; L-HPC-31, 10.0—12.9%) 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.), 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.), erithritol (Nikken Chemicals Co., Ttd.), and magnesium stearate (Taihei

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Chemical Industrial Co., Ltd.) were purchased. Yellow ferric oxide (Anstead International Co., Ltd.) and red ferric oxide (BASF Japan Ltd.) were used as the pigments. All other excipients used in the dosage forms are specified in the Japanese Pharmacopoeia (JP) and Japanese Pharmaceutical Excipients.

Viscosity of L-HPC Suspension Sixty grams of accurately weighed L-HPC was transferred to 600 ml of purified water in dissolution apparatus 2 (paddle) and suspended at 200 rpm for 30 min. The purified water was previously kept at 25±0.5 °C. Viscosity of the suspension was measured using a digital viscometer (Type DVL-BII, Tokimec Inc., Japan). The viscosity was measured three times.

Sensory Evaluation of Roughness of L-HPC Sensory tests of the threshold value of the roughness of L-HPC-31 were carried out in 6 volunteers. After the mouth was rinsed with purified water, L-HPC-31 10—40 mg was held in the mouth for *ca.*10 s and spat out, and the mouth was rinsed again. Results showed the roughness threshold weight to be 20 mg. Sensory evaluation of the roughness of different L-HPC 30 mg was then carried out and the roughness level recorded. A numerical scale was used with the following values: 0, no roughness; 1, slight roughness; and 2, roughness.

Sensory Evaluation of Disintegration and Roughness of Tablets Flat-faced direct-compression tablets 300 mg in weight and 10 mm in diameter were prepared using a rotary tablet press (Correct 12 HUK, Kikusui Seisakusho, Ltd., Japan) at compression force of 9.8 kN/cm^2 and compression speed of 30 rpm, as shown in Table 1.

Sensory tests of roughness and disintegration of tablets were carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth for 60 s and then spat out, and the mouth was rinsed again. The roughness level and the dissolution level were recorded. A numerical scale was used with the following values: 0, no roughness; 1, slight roughness; and 2, roughness; and 0, rapidly; 1, moderately; 2, slowly, and 3, not disintegrated.

Preparation of LFDT LFDT consist of enteric-coated microgranules (mean particle size, approximately 300 μm) containing lansoprazole and inactive granules. Previously we reported the design of the enteric-coated microgranules.[21,22] We had to resolve the three issues of damage to the enteric layer during the compression process, the unpleasant bitter taste of triethyl citrate, and the poor stability of lansoprazole in the enteric-coated microgranules. Finally we developed enteric-coated microgranules comprising seven layers: 1) core, 2) active compound layer, 3) intermediate layer (stabilization of lansoprazole), 4) first enteric layer (stabilization of lansoprazole), 5) second enteric layer (reduction of damage to the enteric layer during the compression process), 6) third enteric layer (masking the unpleasant bitter taste), and 7) overcoating layer (preventing agglomerates of enteric-coated microgranules during the drying process) with improved oral acceptance, sufficient flexibility of the enteric layers against compression, and improved stability of lansoprazole.

Coating of Active Compound Layer and Intermediate Layer Table 2 presents the formulation in the preparation of lansoprazole-coated microgranules. An active compound suspension consisting of lansoprazole, magnesium carbonate, L-HPC-32, hydroxypropyl cellulose, and purified water was prepared by stirring. An intermediate suspension consisting of hydroxypropyl methycellulose 2910, L-HPC-32, talc, titanium dioxide, mannitol, 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 3 lists the operating conditions for coating. The above granules were dried in the rotating fluidized-bed granulator.

Coating of the Enteric Layer Table 2 presents 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 in 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 overcoating solution consisting of mannitol and purified water was prepared by stirring.

Lansoprazole-coated microgranules were coated consecutively by spraying two-thirds part of the first enteric coating suspension, the second enteric coating suspension, the remaining one-third of the first enteric coating suspension, and the overcoating solution in the rotating fluidized-bed granulator. Table 3 lists the operating conditions for coating. The above granules were then dried in the rotating fluidized-bed granulator.

Table 1. Formulation of Tablets

Erithritol		239.1 mg
Low-substituted hydroxypropyl cellulose		60.0 mg
Magnesium stearate		0.9 mg
	Total	300.0 mg

Preparation of LFDT Table 4 presents the formulations in the preparation of the inactive granules. A binder solution consisting of mannitol, citric acid, and purified water was prepared by stirring. Mannitol, L-HPC-33, microcrystalline cellulose, crospovidone, and aspartame were granulated by spraying the binder solution into a fluid-bed granulator (FD-3S, Powrex Co., Ltd., Japan). Table 5 lists the operating conditions for the granulation. The above granules were then dried in the fluid-bed granulator.

The enteric-coated microgranules, the inactive granules, flavoring, and magnesium stearate were mixed in the weight ratios shown in Table 4. The mixed granules were compressed with a rotary tablet press (Correct 12HUK, Kikusui Seisakusho, Ltd., Japan). Tablets 420, 570, and 720 mg in weight, and 12 mm in diameter were prepared at 30 rpm compression speed and 20 kN/cm^2 compression force. Tablets 570 mg in weight and 12 mm in diameter were prepared at 30 rpm compression speed and at three different compression forces (20, 25, and 30 kN/cm^2).

Tablet Tensile Strength The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a tablet hardness tester (Toyama Sangyo Co., Ltd., Japan). The test was performed in 10 runs and the average was calculated. Tensile strength for crushing (T) was calculated using the following equation: $T=2F/(\pi dt)$, where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Disintegration Time in the Mouth Measurements of disintegration time in the mouth were carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth until the tablet disintegrated without chewing and then spat out, and the mouth was rinsed again. The disintegration time was recorded.

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).

Results and Discussion

Effect of Hydroxypropoxy Group Content in L-HPC on the Qualities of LFDT Watanabe *et al.*[12] reported that tablets prepared with microcrystalline cellulose and L-HPC rapidly disintegrated in saliva. However, it was indicated that patients sometimes sensed roughness in the mouth due to the incomplete solubilization of this type of tablet in saliva.[17] In the design of the inactive granules, microcrystalline cellulose, L-HPC, and crospovidone were used as binders and disintegrants. These water-insoluble excipients have a very rough texture and it was thought that their particle size and the water absorption properties might result in the rough texture. Water-insoluble excipients with small particle size are smoother than water-insoluble excipients with large particle size. Ishikawa *et al.*[14] noted the relationship between the particle size of microcrystalline cellulose and rough texture and

Table 2. Formulation of Enteric-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 (L-HPC-32)	5.0 mg
	Hydroxypropyl cellulose	10.0 mg
	Purified water[a)]	128 μl
Intermediate layer	Hydroxypropyl methycellulose 2910	7.0 mg
	Low-substituted hydroxypropyl cellulose (L-HPC-32)	5.0 mg
	Talc	3.0 mg
	Titanium dioxide	3.0 mg
	Mannitol	7.0 mg
	Purified water[a)]	100 μl
Enteric layer 1	Methacrylic acid copolymer dispersion[b)]	15.26 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b)]	1.7 mg
	Macrogol 6000	1.7 mg
	Glyceryl monostearate	1.0 mg
	Polysorbate 80	0.3 mg
	Citric acid	0.02 mg
	Pigment	0.02 mg
	Purified water[a)]	70 μl
Enteric layer 2	Methacrylic acid copolymer dispersion[b)]	84.0 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b)]	9.33 mg
	Triethyl citrate	18.7 mg
	Glyceryl monostearate	6.0 mg
	Polysorbate 80	1.8 mg
	Citric acid	0.05 mg
	Pigment	0.12 mg
	Purified water[a)]	142 μl
Enteric layer 3	Methacrylic acid copolymer dispersion[b)]	7.63 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b)]	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[a)]	35 μl
Overcoating layer	Mannitol	10.0 mg
	Purified water[a)]	60 μl
	Total	270.0 mg

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

Table 3. Operating Conditions for Enteric-Coated Microgranules

	Active compound layer	Intermediate layer	Enteric layer	Overcoating layer
Total charge amount (kg)	2.55	3.3	3.12	3.24
Inlet air volume (m^3/min)	1.0	1.5	1.5	1.5
Inlet air temperature (°C)	65	75	75	75
Product temperature (°C)	*ca.* 30	*ca.* 40	*ca.* 40	*ca.* 40
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

reported a new type of rapidly disintegrating tablet with good texture using microcrystalline cellulose with small particle size and spherical sugar granules. On the other hand, patients sense roughness when some water-insoluble excipient remains in powder form in the mouth after it absorbs saliva.

The rough texture was evaluated as more unpleasant in the order L-HPC>crospovidone>microcrystalline cellulose. The improvement of the rough texture of L-HPC was thus attempted from the viewpoint of water absorption properties. In this study, we selected the small particle sizes (mean particle size, approximately 25 μm) of L-HPC because they are smoother than large particle sizes (mean particle size, approximately 40 μm). There are three grades of L-HPC with different water absorption properties based on different hydroxypropoxy group content.[23)] The water absorption properties of L-HPC were evaluated by viscosity measurement of L-HPC suspension. The viscosity decreased markedly with decreasing hydroxypropoxy group content, as shown in Fig. 1. It was thought that L-HPC with hydroxypropoxy group content lower than L-HPC-32 might decrease the water absorption capacity of L-HPC. A new grade of L-HPC (L-HPC-33), in which the hydroxypropoxy group content is

Table 4. Formulations of LFDT

Content of enteric-coated microgranules	37.5%	47.4%	64.3%
Enteric-coated microgranules	270.0 mg	270.0 mg	270.0 mg
Inactive granules			
Mannitol	102.0 mg	204.0 mg	306.0 mg
Low-substituted hydroxypropyl cellulose (L-HPC-33)	15.0 mg	30.0 mg	45.0 mg
Microcrystalline cellulose	15.0 mg	30.0 mg	45.0 mg
Crospovidone	7.5 mg	15.0 mg	22.5 mg
Citric acid	1.5 mg	3.0 mg	4.5 mg
Aspartame	4.5 mg	9.0 mg	13.5 mg
Purified water[a)]	22.5 μl	45 μl	67.5 μl
Flavor	1.5 mg	3.0 mg	4.5 mg
Magnesium stearate	3.0 mg	6.0 mg	9.0 mg
Total	420.0 mg	570.0 mg	720.0 mg

a) Removed during processing.

Table 5. Operating Conditions for Inactive Granules

Total charge amount (kg)	2.91
Inlet air volume (m^3/min)	1.0
Inlet air temperature (°C)	65
Product temperature (°C)	*ca.* 25
Atomizing air volume (Nl/min)	80
Spray rate (g/min)	*ca.* 20

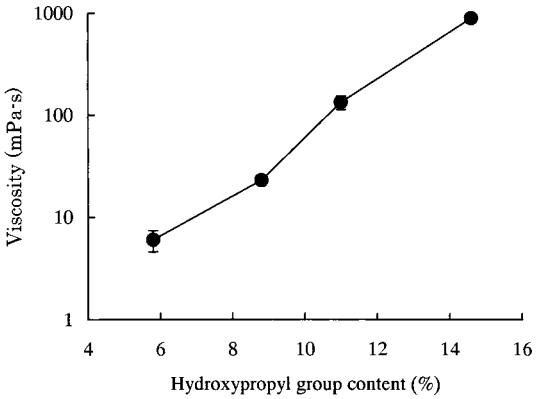

Fig. 1. Relationship between the Hydroxypropoxy Group Content of L-HPC and the Viscosity of the L-HPC Suspension

Data are expressed as mean±S.D. (n=3).

5.0—6.9, was developed in cooperation with Shin-Etsu Chemical Co., Ltd., and the L-HPC-33 suspension exhibited the lowest viscosity, as shown in Fig. 1. The data demonstrated that the capacity of water absorption of L-HPC-33 decreased as compared with other grades.

We also evaluated the rough texture by sensory evaluation and disintegration in the mouth using the tablets with the formulations shown in Table 1. The results are given in Table 6. The tablets comprised of L-HPC-32 and L-HPC-33 exhibited rapid disintegration in the mouth and those comprised of L-HPC-31 and L-HPC-30 did not disintegrate in the mouth. The data demonstrate that L-HPC-32 and L-HPC-33 with lower hydroxypropoxy group content are useful as the binder and disintegrant for tablets that disintegrate rapidly in the mouth. Only L-HPC-33 had a smooth texture. The others did not result in a proportional improvement of the rough texture with the decrease in the viscosity of L-HPC suspension because the water absorption capacity is too great compared to saliva secretion. The data suggest that a decrease in the water absorption properties of L-HPC and a decrease in the combined amount of water-insoluble excipients could improve the rough texture. Based on the results, L-HPC-33 with the lowest hydroxypropoxy group content was superior to the others in terms of roughness and disintegration in the mouth.

The effects of hydroxypropoxy group content in L-HPC on the qualities of tablets and rough texture of the rapidly disintegrating tablets containing enteric-coated microgranules were investigated. Tablets 360 mg in weight and 12 mm in diameter were prepared using a rotary tablet press at compression force of 25 kN/cm^2 and 30 rpm compression speed, as shown in Table 7. The tensile strength, disintegration time in the mouth, and roughness were evaluated, as shown in Table 7. The tensile strength of tablets comprised of L-HPC-33 was similar to that of tablets comprised of L-HPC-31. The disintegration time in the mouth of tablets comprised of L-HPC-33 was shorter than that of tablets comprised of L-HPC-31. The texture of tablets comprised of L-HPC-33 was smoother than that of tablets comprised of L-HPC-31. Based on these results, L-HPC-33 with the lowest hydroxypropoxy group content is the most suitable binder and disintegrant for LFDT.

Effect of Enteric-Coated Microgranule Content on Qualities of LFDT Various researchers have reported the effects of various excipients, particle size of coated pellets, coating level, and pellet content on drug release and crushing force in sustained-release formulations.[24—29)] Beckert *et al.*[30)] investigated the influence of compression force, excipients, pellet content, and coating formulation on the dissolved percentage in the acid stage and the disintegration time of rapidly disintegrating tablets containing enteric-coated pellets. They concluded that the dissolved percentage in the acid stage increased with the increasing content of enteric-coated pellets. Lehmann *et al.*[31)] reported the effects of compression on dissolution behavior in the buffer stage after acid-resistance tests on tablets containing enteric-coated pellets.

In the development of LFDT, we aimed for sufficient tensile strength not to be damaged during ejection from the package, rapid disintegration in the mouth, and dissolution behavior in the acid and buffer stages similar to that of current lansoprazole capsules. We set the desirable tensile strength at not less than 30 N/cm^2 and the desirable disintegration time in the mouth at not more than 30 s. To achieve these goals, it was necessary to determine the suitable enteric-coated microgranule content in LFDT. Three LFDTs

Table 6. Effects of Hydroxypropoxy Group Content in L-HPC on Sensory Evaluation

Hydroxypropoxy group content (grade)	Volunteer	5.8% (L-HPC-33)	8.8% (L-HPC-32)	11.0% (L-HPC-31)	14.6% (L-HPC-30)
Disintegration[a)]	A	0	0	3	3
	B	0	0	3	3
	C	0	0	3	3
	D	1	1	3	3
	E	0	0	3	3
	F	0	0	3	3
	Mean	0.17	0.17	3	3
Rough texture[b)]	A	0	2	2	2
	B	0	1	2	2
	C	0	2	2	2
	D	0	2	2	2
	E	0	2	2	2
	F	1	2	2	2
	Mean	0.17	1.83	2	2

a) 0, rapidly; 1, moderately; 2, slowly; 3, not disintegrated. *b*) 0, no roughness; 1, slight roughness; 2, rough.

Table 7. Formulation and Effect of Hydroxypropoxy Group Content in L-HPC on the Quality of LFDT

Hydroxypropoxy group content (grade)	5.8% (L-HPC-33)	11.0% (L-HPC-31)
Enteric-coated microgranules	135.0 mg	135.0 mg
Erythritol	181.5 mg	181.5 mg
Low-substituted hydroxypropyl cellulose	33.75 mg	33.75 mg
Microcrystalline cellulose	6.75 mg	6.75 mg
Citric acid	2.25 mg	2.25 mg
Magnesium stearate	0.75 mg	0.75 mg
Total	360.0 mg	360.0 mg
Tensile strength[a)]	48.3±2.0 N/cm^2	45.3±1.6 N/cm^2
Disintegration time in the mouth		
Volunteer A	22 s	46 s
B	36 s	63 s
C	33 s	61 s
D	30 s	52 s
E	24 s	48 s
F	28 s	56 s
Mean±S.D.	28.8±5.0 s	54.0±6.9 s
Sensory evaluation[b)]		
Volunteer A	0	1
B	0	1
C	0	2
D	0	0
E	1	2
F	0	1
Mean	0.17	1.17

a) Data are expressed as mean±S.D. (n=10). *b*) 0, no roughness; 1, slight roughness; 2, rough.

were prepared by varying the content of enteric-coated microgranules, as shown in Table 4. The tensile strength, disintegration time in the mouth, and dissolution in the acid and buffer stages were evaluated, as shown in Table 8 and Fig. 2.

The tensile strength decreased and the disintegration time in the mouth was more rapid with the increase in the enteric-coated microgranule content in LFDT. The data demonstrate that a 47.4% content enteric-coated microgranules conferred the predetermined desirable qualities on LFDT.

The dissolved percentage in the acid stage increased and the dissolution in the buffer stage slightly decreased with the increase in the enteric-coated microgranule content in LFDT. The cleavage and crushing of the enteric layer occurred with the decrease in the combined amount of inactive granules that played a role in cushioning during compression. Since ethyl acrylate-methyl methacrylate copolymer dispersion and triethyl citrate have strong cohesion forces, the cohesion forces of the enteric-coated microgranules were enhanced with the decrease in the distance between the enteric-coated microgranules, and the enteric-coated microgranules delayed the disintegration of agglomerates during the dissolution test in the buffer stage with the increase in the enteric-coated microgranule content. The dissolved percentage of lansoprazole capsules in the acid stage was no more than 3% and the dissolution profiles of lansoprazole capsules in the buffer stage were similar to those of LFDT in which the content of the enteric-coated microgranules was set at 37.5% and 47.4%. Therefore 47.4% content of enteric-coated microgranules in LFDT was selected.

Effects of Compression Force on Qualities of LFDT LFDT with a 47.4% enteric-coated microgranule content were prepared by varying the compression force. The tensile

Table 8. Effects of Enteric-Coated Microgranule Content on the Qualities of LFDT

Enteric-coated microgranule content	37.5%	47.4%	64.3%
Tensile strength (N/cm^2)	51.6±1.6	32.4±2.0	12.0±0.8
Disintegration time in the mouth (s)	49.2±9.6	26.8±6.7	9.7±2.6
Dissolved percentage in the acid stage (%)	0.4±0.1	2.5±0.3	11.0±0.6

Data are expressed as mean±S.D. (n=6).

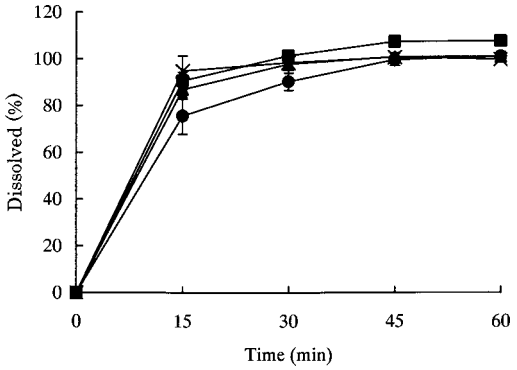

Fig. 2. Effect of Enteric-Coated Microgranule Content on Dissolution in the Buffer Stage

Data are expressed as mean±S.D. (n=6). ×, Lansoprazole capsules. Enteric-coated microgranule content: ■, 37.5%; ▲, 47.4%; ●, 64.3%.

Table 9. Effects of Compression Forces on the Qualities of LFDT

Compression force (kN/cm^2)	20	25	30
Tensile strength (N/cm^2)	25.3±0.3	38.2±0.6	41.8±0.7
Disintegration time in the mouth (s)	30.3±7.9	33.2±5.6	46.3±8.1
Dissolved percentage in the acid stage (%)	3.0±0.4	2.7±0.2	2.7±0.4

Data are expressed as mean±S.D. (n=6).

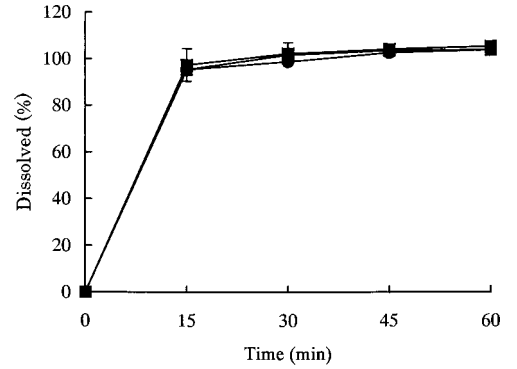

Fig. 3. Effect of Compression Forces on Dissolution in the Buffer Stage

Data are expressed as mean±S.D. (n=6). Compression force: ■, 20 kN/cm^2; ▲, 25 kN/cm^2; ●, 30 kN/cm^2.

strength, disintegration time in the mouth, and dissolution were evaluated, as shown in Table 9 and Fig. 3. The tensile strength increased and disintegration time in the mouth was slower with the increase in compression force. Compression force did not affect the dissolved percentage in the acid stage and dissolution profiles in the buffer stage. The data suggest that the enteric-coated microgranules have sufficient flexibility of the enteric layer and the inactive granules prevent enhancement of the cohesion forces of the enteric-coated microgranules.

Conclusions

To develop rapidly disintegrating tablets containing enteric-coated microgranules, methods to improve of the rough texture of the L-HPC used as a binder and disintegrant were examined. The new grade L-HPC-33 (hydroxypropyl group content, 5.0—6.9%) has no rough texture due to decreased water absorption. L-HPC-33 could thus be useful as a binder and disintegrant in rapidly disintegrating tablets.

The enteric-coated microgranule content in LFDT affected tensile strength, disintegration time in the mouth, and dissolution behavior in the acid and buffer stages. The desirable microgranule content of 47.5% was selected to achieve the desirable qualities of LFDT. Compression force affected tensile strength and disintegration time in the mouth, but did not affect dissolution behavior in the acid and buffer stages. The data suggest that the enteric-coated microgranules were not affected by impulsive force such as compression force with an appropriate enteric-coated microgranule content in LFDT.

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