# Formulation Study for Lansoprazole Fast-disintegrating Tablet. I. Effect of Compression on Dissolution Behavior

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**Lansoprazole fast-disintegrating tablet (LFDT) is a new patient-friendly formulation of lansoprazole. Since lansoprazole is an antiulcer agent and is unstable under acidic conditions, we have developed LFDT as an orally disintegrating tablet containing enteric-coated microgranules. The effect of compression on dissolution behavior was investigated, as compression affected cleavage and crushing of the enteric layer. To decrease cleavage and crushing of the enteric layer, the effects of the combined ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion and the concentration of triethyl citrate on the dissolution in the acid stage and the dissolution in the buffer stage were evaluated. By adjusting the ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion to 9 : 1 and adding a 20% triethyl citrate concentration, sufficient flexibility of the enteric layer and sufficient stability against compression forces were achieved. Agglomeration of enteric-coated microgranules during the coating process was decreased at the optimized concentration of triethyl citrate and glyceryl monostearate. We compared the absorption properties of LFDT and lansoprazole capsules in dogs. The absorption profiles of LFDT were similar to those of lansoprazole capsules.**

**Key words** fast-disintegrating tablet; lansoprazole; acid resistance; dissolution

Enteric dosage forms have two type of systems. One is a single unit and the other is a multiple unit. Most enteric-coated tablets are a formulation of a single unit. Generally, these tablets are small but can be affected by the interdigestive migrating complex (IMC) that can negatively influence absorption.[1—6] The multiple unit improves the shortcomings of the single unit. Common formulations of the multiple unit include capsules or tablets containing enteric-coated granules. Granules contained in these capsules or tablets are less affected by the IMC and consequently absorption issues are minimized.[6,7] However, these capsules and tablets are relatively large in size compared to the single unit; in rare cases, some patients may find the capsules and tablets difficult to swallow. Therefore it is necessary to improve patient swallowing when developing enteric dosage forms of the multiple unit.

Lansoprazole, a substituted benzimidazole, is a highly specific inhibitor of gastric ($H^+ + K^+$)-ATPase.[8,9] This compound is unstable under acidic conditions. Lansoprazole was developed as a capsule containing enteric-coated granules,[7,10—13] and we have therefore tried to improve its ease of swallowing by patients.

The purpose of this study was to develop enteric-coated microgranules for a new, patient-friendly formulation, which improves the swallowing while maintaining the merits of the multiple unit. In this study, we particularly aimed to determine any damage to the enteric layer during compression and to reduce cleavage and crushing of the enteric layer by designing a flexible enteric layer.

## 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 $\mu$m) 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.), 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. All other excipients used in the dosage forms are specified in the *Japanese Pharmacopoeia* (JP) and *Japanese Pharmaceutical Excipients*.

**Preparation of Lansoprazole Fast-disintegrating Tablets** The conceptual scheme of lansoprazole fast-disintegrating tablets (LFDT) is provided in Chart 1. LFDT consists of enteric-coated microgranules containing lansoprazole and inactive granules.

**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, magnesium carbonate, low-substituted hydroxypropyl cellulose (LH-32), hydroxypropyl cellulose, and purified water was prepared by stirring. An intermediate suspension consisting of hydroxypropyl methylcellulose 2910, others, and purified water was prepared by stirring. Lactose monohydrate-microcrystalline cellulose spheres were coated consecutively by spraying the

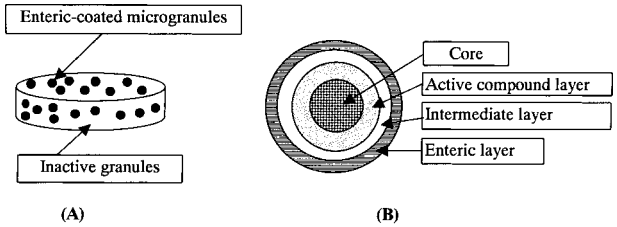


Chart 1. Structure of Lansoprazole Fast-Disintegrating Tablets (A) and Cross Section of Enteric-Coated Microgranules (B)

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Table 1. Formulation of Lansoprazole-Coated Microgranules

| | | | |
|---|---|---|---|
| Core | Lactose monohydrate–microcrystalline cellulose spheres | | 30 mg |
| Active compound layer | Lansoprazole | | 30 mg |
| | Magnesium carbonate | | 10 mg |
| | Low-substituted hydroxypropyl cellulose (LH-32) | | 5 mg |
| | Hydroxypropyl cellulose | | 10 mg |
| | Purified water[a)] | | 128 μl |
| | | Subtotal | 85 mg |
| Intermediate layer | Hydroxypropyl methycellulose 2910 | | 9.5 mg |
| | Other[b)] | | 0.5 mg |
| | Purified water[a)] | | 40 μl |
| | | Total | 95 mg |

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

Table 2. Operating Conditions for Enteric-Coated Microgranules

| | Active compound layer | Intermediate layer | Enteric layer |
|---|---|---|---|
| Total charge amount (kg) | 0.9—2.6 | 0.8—2.6 | 1.0—3.6 |
| Inlet air volume ($m^3$/min) | 1.0 | 1.5 | 1.5 |
| Inlet air temperature (°C) | 70—85 | 70—85 | 65—80 |
| Product temperature (°C) | *ca.* 30 | *ca.* 40 | *ca.* 40 |
| Atomizing air volume (Nl/min) | 80 | 100 | 100 |
| Spray rate (g/min) | *ca.* 20 | *ca.* 15 | *ca.* 20 |
| Rotor speed (rpm) | 500 | 550 | 600 |

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** Table 3 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 with a dispersing machine. An enteric-coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate–methyl methacrylate copolymer dispersion, the glyceryl monostearate emulsion, plasticizer (triethyl citrate or macrogol 6000), talc, and purified water was prepared by stirring.

Lansoprazole-coated microgranules were coated by spraying the enteric coating suspension in the rotating fluidized-bed granulator. The above granules were then dried in the rotating fluidized-bed granulator.

**Preparation of LFDT** The enteric-coated microgranules, mannitol, low-substituted hydroxypropyl cellulose (LH-33), microcrystalline cellulose, crospovidone, others, and magnesium stearate were mixed at the weight ratio shown in Table 4. The mixed granules were compressed with a rotary tablet press (Correct 12HUK, Kikusui Seisakusho, Ltd., Japan). Tablet of 500 mg and 11 mm in diameter were prepared at 30 rpm compression speed and 14.7 kN/$cm^2$ compression force.

**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 2 stages.

Acid Stage: Five hundred milliliters of 0.1 N HCl was used as the dissolution medium. 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).

**Level of Agglomerates** Fifty grams of enteric-coated microgranules were weighed out. The macrogranules were tapped 300 times in sieves with mesh size of 250 μm and 350 μm. The residual sample on the 250-μm or 350-μm sieve and the sample that passed through the 250-μm sieve were weighed, and the proportion of the gross weight was calculated.

**Absorption Study in Dogs** Four healthy male beagle dogs were used in this study. Pentagastrin was administered hypodermically 60 min before dosing with lansoprazole.[7)] Capsules (equivalent to lansoprazole 30 mg) were administered orally to each dog with 20 ml of water under fasting conditions. LFDT was administered orally to each dog without water under fasting conditions. This study was carried out in a crossover fashion. Venous blood samples (2.5 ml) were collected 0.25, 0.5, 1, 1.5, 2, 3, 5, and 8 h after dosing with lansoprazole and immediately centrifuged. The plasma samples were kept frozen at −20 °C until assayed. Lansoprazole in the plasma was determined using the HPLC method.[14)]

## Results and Discussion

**Effect of Compression on Enteric-Coated Microgranules** Since LFDT comprises enteric-coated microgranules and inactive granules, it was thought that compression might affect cleavage and crushing of the enteric layer. Methacrylic acid copolymer dispersion was selected as an enteric film former. This polymer forms brittle films that cannot withstand compression forces.[15,16)] In practice, enteric-coated microgranules based on the recommendations of the manufacturer[17)] were prepared, as shown in Table 3 (formulation no. 1). We selected a 40% concentration of enteric-coated microgranules in LFDT, as shown in Table 4. The dissolved percentage after 60 min in the acid stage and dissolution in the buffer stage were measured to evaluate the damage occurring during the compression process. The mean dissolved percentage of enteric-coated microgranules and LFDT in the acid stage was 0.4% and 9.9%, respectively, and it was confirmed that the mean dissolved percentage of LFDT in the acid stage increased during compression compared with that of enteric-coated microgranules. The results suggested that cleavage and crushing of the enteric layer occurred during compression. The dissolved percentage of lansoprazole from enteric-coated microgranules in the buffer stage was almost 100% after 15 min. Therefore the increase in flexibility of the enteric layer is essential to minimize the damage, and the damage can be evaluated using the dissolved percentage in the acid stage (acid resistance test).

**Improvement in Cleavage and Crushing of Enteric Layer during Compression** Talc is widely used in oral solid-dosage formulations as a lubricant and diluent. We also used talc as an antiagglomerating agent in the enteric layer. Since inorganic material, such as talc, was anticipated to increase the damage to the enteric layer during compression, it was considered important to decrease the amount of talc. Glyceryl monostearate was therefore chosen as the antiagglomerating agent instead of talc. Furthermore, we studied two ingredients that increase the flexibility of the enteric layer: ethyl acrylate–methyl methacrylate copolymer dispersion and a type of plasticizer.

**Effect of the Ratio of Methacrylic Acid Copolymer Dispersion to Ethyl Acrylate–Methyl Methacrylate Copolymer Dispersion on Acid Resistance and Buffer Dissolution** Ethyl acrylate–methyl methacrylate copolymer dispersion is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methylmethacrylate.[18)] As its softening temperature is *ca.* 12 °C, as measured by thermomechanical analysis (TMA), it forms a film of sufficient flexibility and high elongation at break point.[15,19)] Furthermore, it is com-

Table 3. Formulations of Enteric-Coated Microgranules

Effect of the ratio of methacrylic acid copolymer dispersion and ethyl acrylate–methyl methacylate copolymer dispersion on acid resistance and buffer dissolution

| Formulation no. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Methacrylic acid copolymer dispersion : ethyl acrylate–methyl methacrylate copolymer dispersion[d] | 10 : 0 | 9 : 1 | 8 : 2 | 5 : 5 |
| Lansoprazole-coated microgranules[a] | 105.0 mg | 90.0 mg | 90.0 mg | 90.0 mg |
| Enteric layer | | | | |
| Methacrylic acid copolymer dispersion[b] | 60.5 mg | 83.2 mg | 73.9 mg | 46.2 mg |
| Ethyl acrylate–methyl methacrylate copolymer dispersion[b] | — | 9.2 mg | 18.5 mg | 46.2 mg |
| Triethyl citrate | — | 9.2 mg | 9.2 mg | 9.2 mg |
| Macrogol 6000 | 6.0 mg | — | — | — |
| Glyceryl monostearate | — | 3.3 mg | 3.3 mg | 3.3 mg |
| Polysorbate 80 | 2.7 mg | 1.8 mg | 1.8 mg | 1.8 mg |
| Talc | 19.0 mg | 3.2 mg | 3.2 mg | 3.2 mg |
| Pigment | 6.8 mg | 0.1 mg | 0.1 mg | 0.1 mg |
| Purified water[c] | 396.8 μl | 114.4 μl | 114.4 μl | 114.4 μl |
| Total | 200.0 mg | 200.0 mg | 200.0 mg | 200.0 mg |

Effect of concentration of triethyl citrate on acid resistance and buffer dissolution

| Formulation no. | 2 | 5 | 6 | 7 |
|---|---|---|---|---|
| Concentration of triethyl citrate[e] | 10% | 15% | 20% | 30% |
| Lansoprazole-coated microgranules[a] | 90.0 mg | 95.0 mg | 95.0 mg | 95.0 mg |
| Enteric layer | — | — | — | — |
| Methacrylic acid copolymer dispersion[b] | 83.2 mg | 78.3 mg | 75.0 mg | 69.3 mg |
| Ethyl acrylate–methyl methacrylate copolymer dispersion[b] | 9.2 mg | 8.7 mg | 8.3 mg | 7.7 mg |
| Triethyl citrate | 9.2 mg | 13.0 mg | 16.7 mg | 23.0 mg |
| Glyceryl monostearate | 3.3 mg | 3.2 mg | 3.2 mg | 3.2 mg |
| Polysorbate 80 | 1.8 mg | 1.7 mg | 1.7 mg | 1.7 mg |
| Talc | 3.2 mg | — | — | — |
| Pigment | 0.1 mg | 0.1 mg | 0.1 mg | 0.1 mg |
| Purified water[c] | 114.4 μl | 112.0 μl | 120.6 μl | 135.3 μl |
| Total | 200.0 mg | 200.0 mg | 200.0 mg | 200.0 mg |

Reduction of the agglomerates of enteric-coated microgranules

| Formulation no. | 6 | 8 |
|---|---|---|
| Concentration of glyceryl monostearate[f] | 3% | 5% |
| Lansoprazole-coated microgranules[a] | 95.0 mg | 95.0 mg |
| Enteric layer | | |
| Methacrylic acid copolymer dispersion[b] | 75.0 mg | 73.5 mg |
| Ethyl acrylate–methyl methacrylate copolymer dispersion[b] | 8.3 mg | 8.2 mg |
| Triethyl citrate | 16.7 mg | 16.3 mg |
| Glyceryl monostearate | 3.2 mg | 5.2 mg |
| Polysorbate 80 | 1.7 mg | 1.7 mg |
| Pigment | 0.1 mg | 0.1 mg |
| Purified water[c] | 120.6 μl | 124.4 μl |
| Total | 200.0 mg | 200.0 mg |

*a*) Composition of lansoprazole-coated microgranules is the same as shown in Table 1. *b*) Dry lacquer substance. *c*) Removed during processing. *d*) Percentage of the gross solid weight of methacrylic acid copolymer dispersion and ethyl acrylate–methyl methacrylate copolymer dispersion. *e*) Percentage of the gross solid weight of methacrylic acid copolymer dispersion and ethyl acrylate–methyl methacrylate copolymer dispersion. *f*) Percentage of the gross weight of enteric coating ingredients.

monly used in combination with methacrylic acid copolymer dispersion to increase the elasticity of the enteric layer.[15,19,20]

The effects of the ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion on acid resistance and dissolution in the buffer stage were investigated. Three representative formulations of enteric-coated microgranules and LFDT were prepared by varying the ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion as shown in Tables 3 (formulation no. 2—4) and 4. The 60-min acid resistance test and consecutive dissolution profiles of enteric-coated microgranules and LFDT were evaluated. The results obtained are shown in Fig. 1. The dissolved percentage of LFDT in the acid stage decreased as the proportion of ethyl acrylate–methyl methacrylate copolymer dispersion in the mixture increased. Therefore the data suggest that the increased proportion of ethyl acrylate–methyl methacrylate copolymer dispersion can improve the cleavage and crushing of the enteric layer. The dissolution in the buffer stage at ratios of 10 : 0 and 9 : 1 were satisfactory and similar to that of

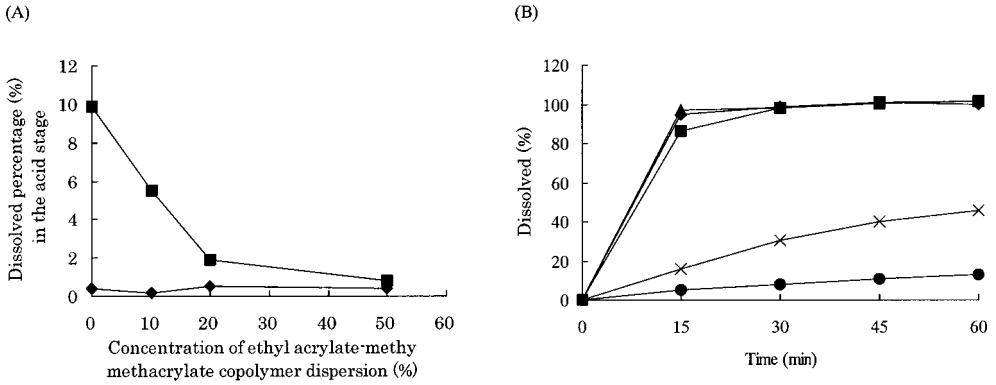


Fig. 1. Effect of the Ratio of Methacrylic Acid Copolymer Dispersion to Ethyl Acrylate–Methyl Methacrylate Copolymer Dispersion on Dissolved Percentage in the Acid Stage and on Dissolution Profiles in the Buffer Stage after 60-min Acid Resistance Test

(A) ◆, Enteric-coated microgranules; ■, LFDT. (B) ◆, Lansoprazole capsules. Ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion: ■, 10 : 0; ▲, 9 : 1; ×, 8 : 2; ●, 5 : 5.

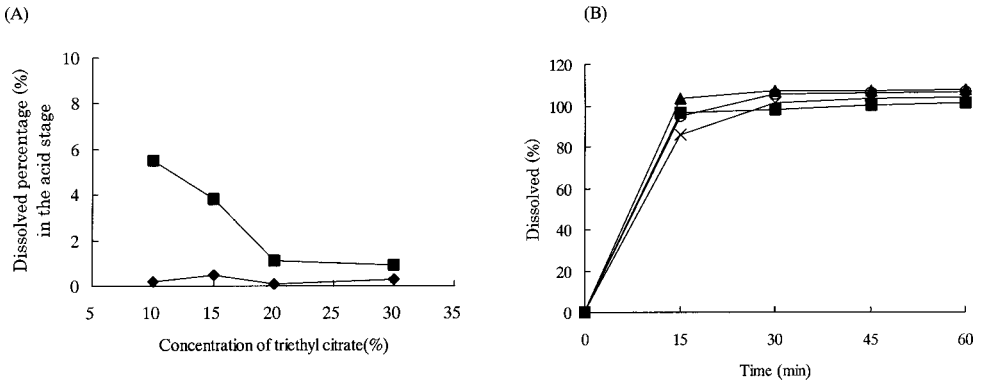


Fig. 2. Effect of Concentration of Triethyl Citrate in the Gross Solid Weight of Methacrylic Acid Copolymer Dispersion and Ethyl Acrylate–Methyl Methacrylate Copolymer Dispersion on Dissolved Percentage in the Acid Stage and on Dissolution Profiles of Enteric-coated Microgranules in the Buffer Stage after 60-min Acid Resistance Test

(A) ◆, Enteric-coated microgranules; ■, LFDT. (B) Concentration of triethyl citrate: ■, 10%; ▲; 15%; ●; 20%; ×, 30%.

lansoprazole capsules; however, the dissolution in the buffer stage at ratios of 8 : 2 and 5 : 5 were unsatisfactory. The cause of the delayed dissolution in the buffer stage was the formation of a water-insoluble film of ethyl acrylate–methyl methacrylate copolymer dispersion, because an insoluble film was observed during the dissolution test in the buffer stage. Consequently, although acid resistance was not optimal, the 9 : 1 ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion was selected in consideration of the dissolution profiles in the buffer stage.

**Effect of Concentration of Triethyl Citrate on Acid Resistance and Buffer Dissolution** Plasticizers are also added to polymeric solutions and dispersions to increase the flexibility and distensibility of the polymeric material.[20—23] Water-soluble plasticizers (triacetin, triethyl citrate, and acetyl triethyl citrate) showed a positive relationship between the concentration of plasticizer and the glass transition temperature depression of methacrylic acid copolymer.[21] However, the increased concentration of the water insoluble plasticizers (tributyl citrate and acetyl tributyl citrate) did not result in a continuous decrease in the glass transition temperature of methacrylic acid copolymer.[21] Therefore the water-soluble plasticizers are thought to be superior to the water-insoluble plasticizer for use at high concentrations. Triethyl citrate was selected among the water-soluble plasticizers in this study. Furthermore, talc, which was contained as an antiagglomerating agent, was deleted.

Table 4. Formulations of LFDT

| | | |
|---|---|---|
| Enteric-coated microgranules | | 200.0 mg |
| Mannitol | | 189.7 mg |
| Low-substituted hydroxypropyl cellulose (LH-33) | | 30.0 mg |
| Microcrystalline cellulose | | 60.0 mg |
| Crospovidone | | 15.0 mg |
| Other | | 2.8 mg |
| Magnesium stearate | | 2.5 mg |
| | Total | 500.0 mg |

Four different formulations of enteric-coated microgranules containing increasing concentrations of triethyl citrate, as shown in Table 3 (formulation no. 2, 5—7) and LFDT, as shown in Table 4, were prepared and the dissolved percentage in the acid stage and the dissolution in the buffer stage were determined. Agglomerates from this manufacturing process were defined as particles of not less than 350 $\mu$m (*i.e.*, the residue on the 350-$\mu$m mesh sieve).

The results of dissolution percentage in the acid stage of enteric-coated microgranules with different concentrations of triethyl citrate and the corresponding LFDT are shown in Fig. 2, the results of dissolution in the buffer stage of enteric-

coated microgranules in Fig. 2, and the levels of agglomerates of enteric-coated microgranules in Fig. 3. The data obtained demonstrated that the formulations with 15%, 20%, and 30% triethyl citrate, as a percentage of the gross solid weight of methacrylic acid copolymer dispersion and ethyl acrylate–methyl methacrylate copolymer dispersion, exhibited improved acid resistance in both the enteric-coated microgranules and LFDT (Fig. 2A). These results suggest that the glass transition temperature was depressed and the brittle character of methacrylic acid copolymer dispersion was reduced with an increase in the concentration of triethyl citrate.

The dissolution in the buffer stage of enteric-coated microgranules with 30% triethyl citrate decreased slightly (Fig. 2B). We observed that the enteric-coated microgranules containing 30% triethyl citrate delayed the disintegration of agglomerates during the dissolution test in the buffer stage. Therefore we assumed that the delay of dissolution in the buffer stage was due to a delay in the disintegration of agglomerates.

Furthermore, the levels of agglomerates increased as the proportion of triethyl citrate increased (Fig. 3). This tendency supports the assumption that cohesion forces of particles were enhanced with increasing triethyl citrate concentration. Based upon these results, 20% triethyl citrate was chosen to achieve sufficient acid resistance and acceptable dissolution in the buffer stage.

**Reduction of Agglomerates of Enteric-Coated Microgranules** Enteric-coated microgranules with satisfactory acid resistance and acceptable dissolution in the buffer stage were developed. However, the formulation required further improvement to reduce the levels of agglomerates during the enteric coating process, as agglomerates reduce the process productivity. Two different formulations of enteric-coated microgranules containing increasing concentrations of glyceryl monostearate, as shown in Table 3 (formulation no. 6, 8), were prepared to reduce the cohesion forces. LFDT containing these enteric-coated microgranules were prepared, as shown in Table 4. The dissolved percentage in the acid stage, dissolution in the buffer stage, and levels of agglomerates were investigated.

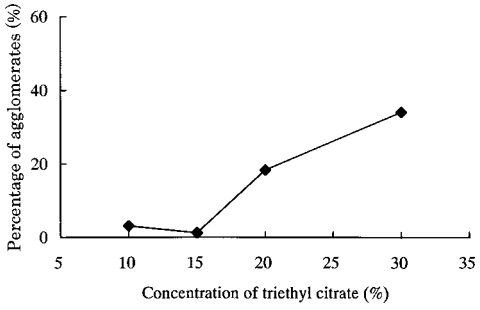


Fig. 3. Effect of Concentration of Triethyl Citrate in the Gross Solid Weight of Methacrylic Acid Copolymer Dispersion and Ethyl Acrylate–Methyl Methacrylate Copolymer Dispersion on Level of Agglomerates

The dissolved percentage in the acid stage of enteric-coated microgranules and LFDT are shown in Fig. 4A, and the dissolution in the buffer stage of enteric-coated microgranules in Fig. 4B. The results demonstrate that the acid resistance in both the enteric-coated microgranules and LFDT and the dissolution in the buffer stage in the enteric-coated microgranules were not affected by increases in the glyceryl monostearate concentration (Fig. 4). However, the level of agglomerates was greatly reduced from 18.3% to 1.5% when the concentration of glycerol monostearate increased from 3% to 5% of the gross weight of the enteric coating ingredients. These results suggest that increases in the antiagglomerating agent decrease the cohesion forces.

**Absorption Study in Dogs** The *in vivo* absorption properties of lansoprazole in dogs were compared between lansoprazole capsules and LFDT containing the enteric-coated microgranules, as shown in Table 3 (formulation no. 8). The results are shown in Fig. 5, and the pharmacokinetic parameters are provided in Table 5. The mean plasma concentration curves after oral administration of LFDT were similar to those of lansoprazole capsules. $C_{max}$ values and $AUC_{0—8\,h}$ values of LFDT were also similar to those of lansoprazole capsules. Tolman *et al.* investigated the effects of oral dosing with lansoprazole on gastric pH.[24] Although there is little evidence of a correlation between $C_{max}$ and the degree of acid suppression, a positive correlation between *AUC* and gastric pH is seen with lansoprazole. Pharmacologic activity is dependent on the extent of lansoprazole absorption rather than on the rate of drug absorption. Therefore a similarity in the *AUC* is a very important factor for the evaluation of pharmacologic activity. Base on the evidence of absorption in dogs, the *AUC* of LFDT agrees with that of lansoprazole capsules. It was confirmed that the pharmacologic activity of LFDT in dogs should be similar to that of lansoprazole capsules. Fur-

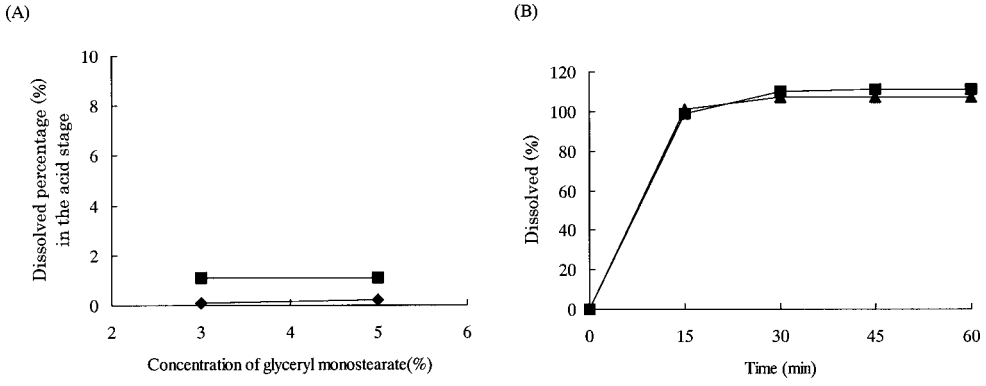


Fig. 4. Effect of Concentration of Glyceryl Monostearate in the Gross Weight of Enteric Coating Ingredients on Dissolved Percentage in the Acid Stage and on Dissolution Profiles of Enteric-coated Microgranules in the Buffer Stage after 60-min Acid Resistance Test

(A) ◆, Enteric-coated microgranules; ■, LFDT. (B) Concentration of glyceryl monostearate: ■, 3%; ▲; 5%.

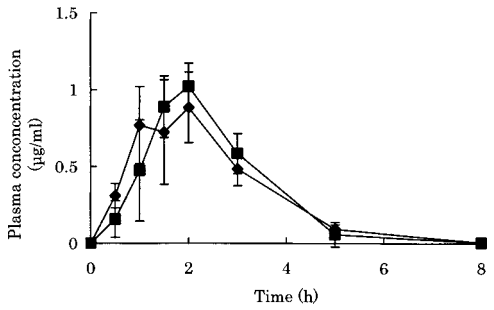


Fig. 5. Comparison of the Absorption of Lansoprazole from Lansoprazole Capsules and LFDT (dose, 30 mg/dog)

The data are expressed as mean±S.E. ($n$=4). ◆, Lansoprazole capsules; ■, LFDT.

Table 5. Pharmacokinetic Parameters of Lansoprazole from Lansoprazole Capsules and LFDT in Beagle Dogs (dose, 30 mg/dog)

| | $T_{max}$ (h) | $C_{max}$ (μg/ml) | $AUC_{0-8\,h}$ (μg·h/ml) |
|---|---|---|---|
| Lansoprazole capsules | 1.8±0.3 | 1.16±0.50 | 2.55±0.95 |
| LFDT | 1.5±0.6 | 1.25±0.44 | 2.55±0.75 |

The data are expressed as mean±S.E. ($n$=4).

thermore, two single-center, open, crossover studies in Japan demonstrated bioequivalence between LFDT taken without water and lansoprazole capsules, at both 15-mg and 30-mg doses.[25)]

## Conclusions

In the development of LFDT, the effects of compression on the dissolution behavior of LFDT were investigated. Compression affected cleavage and crushing of the enteric layer. Sufficient flexibility of the enteric layer with sufficient stability against compression forces can be achieved with a 9 : 1 ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion and by adding a triethyl citrate concentration of 20%. The agglomerates of enteric-coated microgranules decreased with a 20% triethyl citrate concentration and 5% glyceryl monostearate concentration. Furthermore, we compared the absorption and dissolution properties in the buffer stage of LFDT and lansoprazole capsules. The *in vivo* absorption properties of lansoprazole capsules and LFDT were also investigated in dogs. The absorption and dissolution properties in the buffer stage of LFDT were similar to those of lansoprazole capsules.

**Acknowledgments** The authors wish to extend their thanks to Mr. E. Satake and Mr. T. Kashihara for their valuable suggestions in developing this formulation. Acknowledgements also go to Ms. T. Matsuda and Ms. Y. Fujishiro for the assistance in performing assays.

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