DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(9), 1661-1672 (1994)

MANUFACTURING METHOD OF STABLE ENTERIC GRANULES OF A NEW ANTIULCER DRUG (LANSOPRAZOLE)

Tetsuro Tabata*, Tadashi Makino, Jun-ichi Kikuta,
Shinichiro Hirai, Nobuyuki Kitamori

Pharmaceutical Development Laboratories
Production Division, Takeda Chemical Industries, Ltd.,
17-85, Juso-honmachi 2-Chome, Yodogawa-ku, Osaka, 532 (Japan)

Keywords ; lansoprazole, enteric granules, magnesium carbonate, extrusion, CF

SUMMARY

In our previous studies, we clarified that enteric granules are an appropriate dosage form for lansoprazole, and we demonstrated that enteric granules could be produced when magnesium carbonate was added as an alkaline stabilizer.

These granules however were found to be some unstable under severe conditions because some of the excipients are incompatible with lansoprazole. We therefore attempted granulation not using these incompatible excipients and could obtain more stable enteric granules using a centrifugal fluid-bed granulator instead of an extruder-spheronizer. We also compared the absorption and

* To whom correspondence should be addressed.

dissolution properties of the enteric granules manufactured by these two methods.

INTRODUCTION

In our previous studies[1,2], we clarified that the development of enteric granules for lansoprazole was necessary, and we were able to produce stable enteric granules when we added magnesium carbonate as an alkaline stabilizer. Later studies however showed that these granules are not sufficiently stable under severe conditions because some of the excipients used are incompatible with lansoprazole.

In this study, we attempted granulation without these incompatible excipients using a centrifugal fluid-bed granulator instead of an extruder-spheronizer, and we compared the absorption and dissolution properties of the enteric granules manufactured by the two methods.

EXPERIMENTAL METHODS

1. Materials and reagents

Lansoprazole was synthesized at Takeda Chemical Industries, Ltd. Hydroxypropylcellulose JP (type L, hereinafter HPC) and low substituted hydroxypropylcellulose JP (type LH-31, hereinafter L-HPC) were obtained from Nippon Soda Co., Ltd. and Shin-Etsu Chemical Co., Ltd., respectively. All other excipients used in the dosage forms are specified in the Pharmacopoeia of Japan (JP) or Japanese Standards of Pharmaceutical Ingredients.

Triethylamine and phosphoric acid were of reagent grade, and methanol was of analytical grade from Wako Pure Chemical Ind.,Ltd.

2. Manufacturing methods for enteric granules

The manufacturing methods available for production of spherical core granules are extrusion granulation (hereinafter extrusion method) using an extruder-spheronizer and

agglomeration granulation (hereinafter CF method)[3,4] using a centrifugal fluid-bed granulator (hereinafter CF apparatus).

The extrusion method is a conventional method for manufacturing spherical core granules. Lansoprazole was mixed with various excipients (starch, crystalline cellulose, carboxymethylcellulose calcium etc.) and was massed with an aqueous macrogol 6000 solution. This mass was extruded using an extruder, and spherical core granules were formed using a spheronizer. Granules were dried and sieved.

The CF method is a powder coating method. Lansoprazole was mixed with various excipients (sucrose, starch etc.), and nonpareil was coated with the mixture (hereinafter dusting powder) while spraying an aqueous binder solution using a CF apparatus. Granules were dried and sieved.

The core granules were coated with an aqueous enteric suspension using a fluid-bed coater. The enteric coated granules were sieved and dried, and capsules were then filled.

3. Assay of lansoprazole in dosage forms and appearance of dosage forms

To a weighed sample of pulverized dosage form was added 40 ml of methanol followed by sonication for 5 minutes, and to the methanol solution was added 5 ml of the internal standard (40 mg/ml of buthyl paraoxybenzoate in methanol) and 5 ml of methanol. To 1 ml of this solution filtered through a membrane filter (0.45 μ m) was added 9 ml of distilled water. This solution was assayed by high performance liquid chromatography (HPLC) using the conditions shown in Table 1 in comparison with similarly prepared reference standards.

To evaluate the appearance of the dosage form, the color difference in comparison with the control was measured by a color computer (Type SM, Suga Analytical Ltd.) and is shown as ΔE.

4. Dissolution tests (including acid resistance tests)

Dissolution tests were performed in accordance with USP XXII Dissolution 〈711〉 or Drug Release 〈724〉 using apparatus 2 (paddle).

TABLE 1
HPLC conditions

Apparatus	Shimadzu LC-3A
Column	Capcell Pak C_{18} 3.9 mmϕ x 150 mm
Mobile phase	A mixture of methanol, water and triethylamine (60:40:1)
	Adjust the pH to 7.0 with phosphoric acid
Flow rate	1.0 ml/min.
Detector	A UV absorption photometer (wavelength : 285 nm)

First, 500 ml of the 1st Fluid (specified under Disintegration Test in the JP, pH 1.2) was used as the dissolution medium. The dissolution rate after 1 hour was measured. Second, the granules were transferred to 900 ml of the 2nd Fluid (specified under Disintegration Test in the JP, pH 6.8), and medium samples were collected at appropriate intervals. The paddle was driven at 150 rpm.

The amount of drug dissolved in the dissolution medium was determined by a spectrophotometer (acid stage, 306 nm ; buffer stage, 285 nm) after filtering through a membrane filter (0.45μm).

5. Absorption tests and determination of plasma lansoprazole concentration

Enteric granules in a capsule were administered concurrently with 30 ml of water to male beagle dogs (15 - 20 kg) that had been fasted for 24 hours. Blood samples were collected from the fore-limb vein at appropriate intervals.

Collected blood samples (2.5 ml) were immediately centrifuged (3000 rpm x 5 min.) and plasma samples were stored at -20℃ until analysis. To each 1 ml sample of plasma was added an equal volume of saturated sodium bicarbonate solution. This mixture was extracted with 6 ml of dichloromethane, and 5 ml of the extract layer was evaporated to dryness under a stream of nitrogen. The

residue was dissolved in 0.1 ml of the HPLC mobile phase and was chromatographed using the conditions shown in Table 1. Reference standards were prepared similarly using blank plasma spiked at concentrations of 0.5, 1 and 2 μ g/ml.

6. Friability tests

Five grams of granules retained on a sieve (500 μ m) were placed in a stainless steel cylinder (50 ml, 32 mm in diameter) and were shaken in a spex mixer mill (Spex Industries Inc. Type 8000) without a ball for 30 minutes. After sieving with 500 μ m sieve, the retained amount (W g) was weighed. The friability was calculated using equation (1) for evaluation of the hardness of the granules. In addition, disintegration time of the granules was determined according to the method described in the JP.

$$\text{Friability (\%)} = \frac{5 - W}{5} \times 100 \quad \cdots\cdots\cdots\cdots\cdots\cdots (1)$$

RESULTS AND DISCUSSION

1. Comparison of manufacturing methods for stable enteric granules

Fig. 1 shows a comparison of the two manufacturing methods.

Though the extrusion method requires the use of some excipients which are incompatible with lansoprazole (for example macrogol 6000, crystalline cellulose, carboxymethylcellulose calcium etc.)[2], the CF method does not.

Fig. 2 shows a comparison of the stability of the enteric granules manufactured by these two methods when the granules in capsules were stored at 40 ℃ after being packaged in aluminium-laminated film (ZPFP).

The granules manufactured by the extrusion method did not give satisfactory results as there was discoloration after storage at 40℃ for 6 months even though the content was not less than 90%

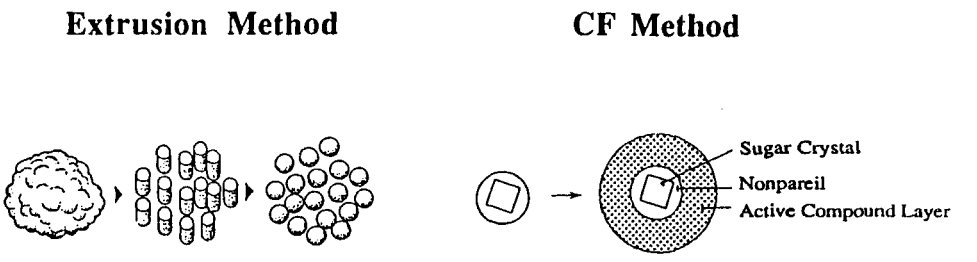

FIGURE 1.
Methods for manufacturing core granules.

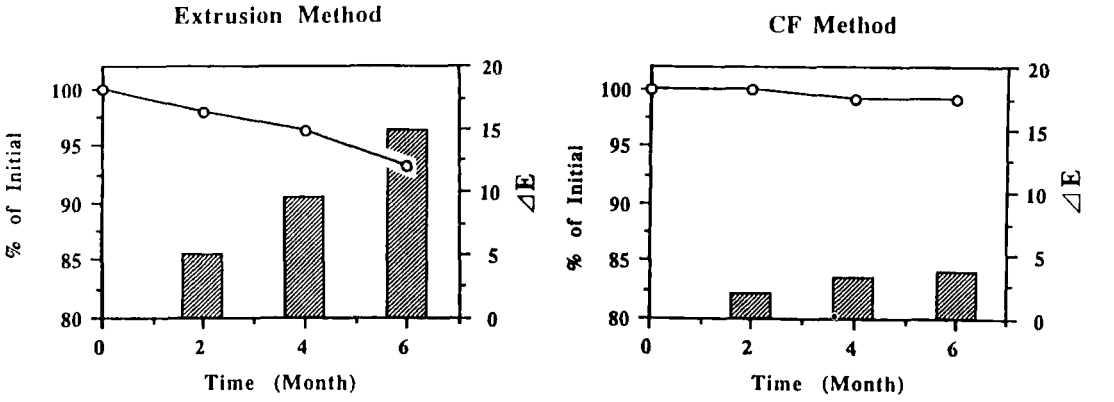

FIGURE 2.
Effect of the manufacturing method on the stability of lansoprazole in enteric granules in capsules stored at 40°C. −○−, % of initial; ▨, ⊿ E of the granules in the capsules.

of the initial. On the other hand, the granules manufactured by the CF method gave satisfactory results because all the excipients needed are compatible with lansoprazole and a stabilizer was added to the granules.

2. Improvement of the manufacturing method for stable enteric granules

Since the CF method involves powder coating while spraying binder solution, the granules manufactured by this method

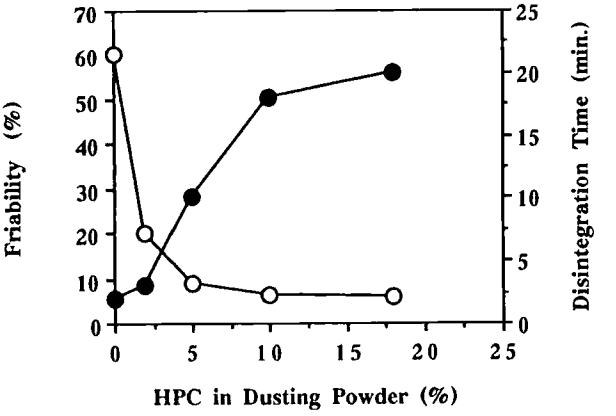

FIGURE 3.
Effect of HPC on the friability
and the disintegration time of lansoprazole core granules.
○, friability; ●, disintegration time.

generally have weak friability. Granules should though have sufficient that they do not break in the next process (enteric coating using a fluid-bed coater). However, when more binder (for example HPC) was used to improve the friability, the disintegration time became longer as shown in Fig. 3. This is not good because rapid disintegration is a general benefit of granules, and enteric granules of lansoprazole should disintegrate rapidly for good absorption properties as described in our previous paper[1]. Therefore, it is necessary to improve the friability without making the disintegration longer.

L-HPC has both the properties of a disintegrant and a binder[5-6]. Fig. 4 shows the friability and disintegration time of the granules manufactured using L-HPC. More than 20% L-HPC in the dusting powder gave sufficient friability without increasing the disintegration time.

Since the granules manufactured by the CF method were more spherical than those manufactured by the extrusion method, they could be coated with the enteric polymer more uniformly.

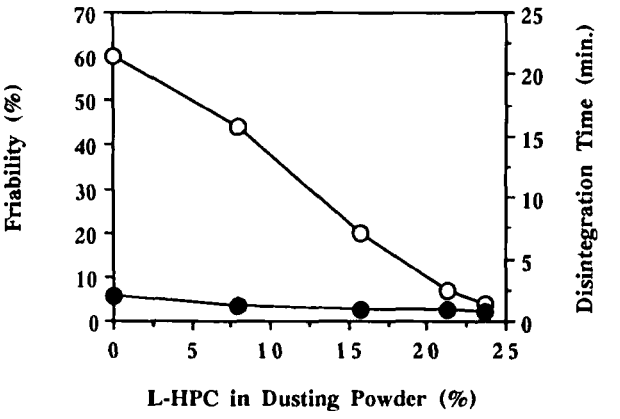

FIGURE 4.
Effect of L-HPC on the friability
and the disintegration time of lansoprazole core granules.
○, friability; ●, disintegration time.

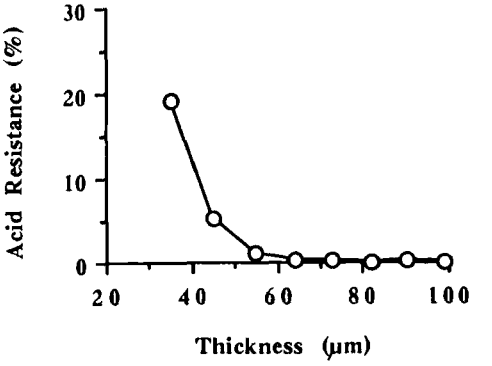

FIGURE 5.
Effect of thickness of the enteric coating layer
on the acid resistance of lansoprazole in enteric granules.

As an enteric polymer, methacrylic acid copolymer LD (Eudragit® L30D-55), which is an aqueous lacquer suspension, was selected for environment and productibility[7-9]. We investigated the effect of thickness of the enteric coating layer on the acid resistance of the enteric granules and the release of

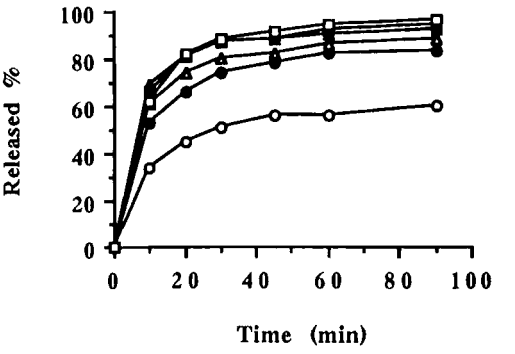

FIGURE 6.

Effect of thickness of the enteric coating layer on the release of lansoprazole from enteric granules.
○, 35 μm; ●, 45 μm; △, 55 μm; ▲, 64 μm; ■, 73 μm; □, 90 μm.

lansoprazole. As shown in Figures 5 and 6, the enteric granules with an enteric coating layer of 35 μm showed that about 20% of lansoprazole was dissolved in the 1st Fluid and consequently more than 60% of that was not dissolved in the 2nd Fluid. However, the thicker enteric coating layer improve the acid resistance and the drug release. As a result, the enteric granules with an enteric coating layer of about 50 μm showed satisfactory acid resistance and drug release profiles.

3. Effects of the manufacturing method on the absorption and dissolution

Effects of the manufacturing method for the enteric granules on the absorption in beagle dogs and the dissolution were examined. Fig. 7 shows the mean plasma concentration curves obtained, Table 2 shows the bioavailability parameters and Fig. 8 shows the mean dissolution profiles after the acid resistance test. There were no significant differences.

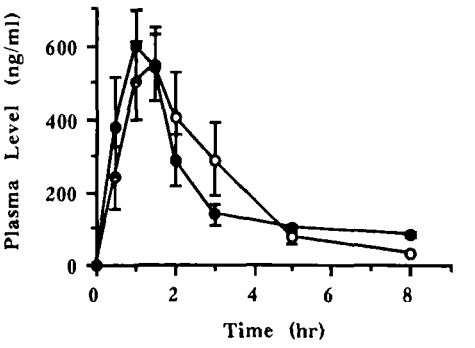

FIGURE 7.
Effect of the manufacturing method on the absorption of lansoprazole in dogs (dose ; 30mg/dog).
○, granules manufactured by the extrusion method;
●, granules manufactured by the CF method.
The data are expressed as mean ± S.E. (n=4).

Table 2
Bioavailability parameters in dogs after oral administration of lansoprazole in enteric granules

Manufacturing Method	Cmax (ng/ml)	Tmax (hr)	AUC(0-8) (ng·hr/ml)
Extrusion	597 ± 91	1.4 ± 0.1	1637 ± 408
CF	648 ± 77	1.3 ± 0.1	1571 ± 234

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

CONCLUSIONS

In our previous studies, we clarified that enteric granules are an appropriate dosage form for lansoprazole, and we could produce stable enteric granules by adding magnesium carbonate as an alkaline stabilizer.

However, since these granules are not sufficiently stable under severe conditions due to the fact that they contain some

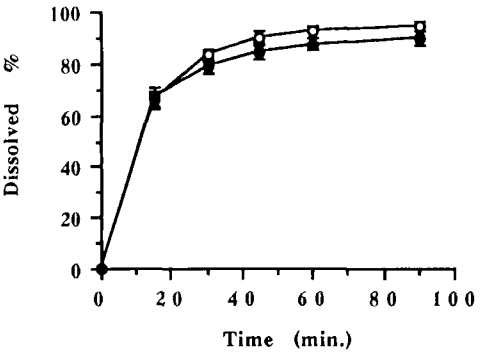

FIGURE 8.

Effect of the manufacturing method on the dissolution of lansoprazole in the granules after a 1 hour acid resistance test.

○, granules manufactured by the extrusion method;

●, granules manufactured by the CF method.

The data are expressed as mean ± S.E. (n=6).

incompatible excipients with lansoprazole, we attempted granulation without using these excipients. We could obtain more stable enteric granules using a centrifugal fluid-bed granulator instead of an extruder-spheronizer. Though the granules manufactured by the CF method generally have the disadvantage of poor friability, the addition of L-HPC gave the granules good friability. We also compared the absorption and dissolution properties of the enteric granules manufactured by the two methods, and there were no significant differences.

REFERENCES

1.Tabata, T., Kashihara, T., Hirai, S., Kitamori, N. and Toguchi, H., J. Biopharm. Sci., 2(4), 319-328 (1991).

2.Tabata, T., Makino, T., Kashihara, T., Hirai, S., Kitamori, N. and Toguchi, H., Drug Develop. Ind. Pharm., 18(13), 1437-1447 (1992).

3.Funakoshi, Y., Yamamoto, M., Matsumura, Y. and Komeda, H., Powder Technology, 27, 13-21 (1980).

4.Ghebre-Sellassie, I., Gordon, R.H., Fawzi, M.B. and Nesbitt, R.U., Drug Develop. Ind. Pharm., 11(8), 1523-1541 (1985).

5. The Pharmacopoeia of Japan 12, D783-786 (1991).

6.Sekigawa, F. and Araume, K., Pharmaceutical Technology, 7, 142-148 (Sep. 1983).

7.Lehmann, K. and Dreher D., Int. J. Pharm. Tech & Prod. Mfr., 2(4), 31-43 (1981).

8.Lehmann, K., Acta Pharm. Fenn., 91, 225-238 (1982).

9.Murthy, K.S., Mahjour, E.M. and Fawzi, M.B., Pharmaceutical Technology, 10, 36-46 (Oct. 1986).