Formulation Approach for Nicorandil Pulsatile Release Tablet

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The purpose of this study was to obtain a nicorandil pulsatile release tablet that has a well-regulated release lag time. When nicorandil is used as an antiangina drug, administration time control is important. A pulsatile release tablet is one of the effective approaches to modified release to reduce daily administration frequency. In this study, a pulsatile release tablet of nicorandil was formulated by fumaric acid dry coating around the core tablet including nicorandil. The model tablets, which had different content ratios of excipients in the dry-coating layer, were characterized by a dissolution test. The results showed that the release lag time was generated with fast release profiles. Various lag time controls of tablets were achieved, from 60 to 310 min on average, by variation of outer layer composition. From an analysis of the relation between lag times and outer layer composition, the key ingredient for prolongation of lag time was found to be fumaric acid. To analyze the lag time generation mechanism, water penetration for tablet was measured. The results indicated that the penetration depth was proportionate to the square root of time and the lag time formation mechanism was simple water penetration through the matrix of fumaric acid to the tablet core. The results also showed that the Washburn equation could be used to design the lag time of the pulsatile release tablet in this study. In conclusion, novel release control technology using fumaric acid was appropriate to obtain a nicorandil pulsatile release tablet that has well regulated lag time.

Key words nicorandil; pulsatile release; tablet; fumaric acid; dry-coating

Various pulsatile release dosage forms have been reported as an approach to improve modified release of existing active ingredients. These dosage forms were intended for drug release in a specific region of the gastrointestinal tract or time dependent release for chronotherapeutics.[1—5] From the technological point of view, most of the dosage forms can be classified as a single-unit type or multiple-unit type. The multiple-unit type is applied when strict time control for release is necessary and rapid release rate is less important. The single-unit type is applied for rapid dissolution after a certain lag time, because it should be possible to avoid deviations in dissolution lag times for each particle.

Nicorandil is a well-known potassium channel modifier used as an antiangina drug.[6] The clinically available dosage form is a tablet with a rapid dissolution profile. In the clinical application of this drug, the frequency of administration is different between Europe and Japan, twice a day for Europe and three times a day for Japan, respectively. Reduction of the administration frequency is desirable but few studies on oral modified release of nicorandil have been reported.

New technology on pulsatile release control was developed to satisfy these requirements.[7] In this research, fumaric acid was used as a release control agent and the shape of tablet was the basic structure as shown in Fig. 1. The tablet is composed of three parts, such as, a core tablet, an outer layer and an initial release part. The core tablet and initial release part contain appropriate doses of nicorandil, respectively. The outer layer of the core tablet was consisted of a dry-coating of fumaric acid, gelatinized corn starch, calcium phosphate anhydrate and some additives without nicorandil. This basic structure enabled the pulsatile release of nicorandil from tablet.

Lag time precision is the most important factor in the clinical application of release type formulations. The purpose of this study was to clarify lag time control factors for appropriate lag time regulation that is the core technology of this formulation. A partial model tablet called the LT (Lag time) tablet was produced to focus on lag time control in this study. The LT tablet, consisting of the core tablet and the outer-layer, releases nicorandil after a certain lag time (Fig. 1). In this study, the effects of ingredients and production conditions on the lag time of the LT tablet were evaluated.

A previous study showed that the drug was released when the outer layer split into two parts after the lag time. Before the split of the outer layer, no significant change on the tablet shape was observed. This observation indicated that erosion did not affect to the lag time. A well-regulated lag time should make it possible to control the time of water penetration into the core tablet. Therefore, the water penetration rate in the outer layer was also investigated and the release mechanism of the LT tablet was analyzed in this study.

Experimental

Materials Nicorandil as the active ingredient and its formulated tablet (Sigmart Tablet 5 mg) were supplied by Chugai Pharmaceutical Co., Ltd.

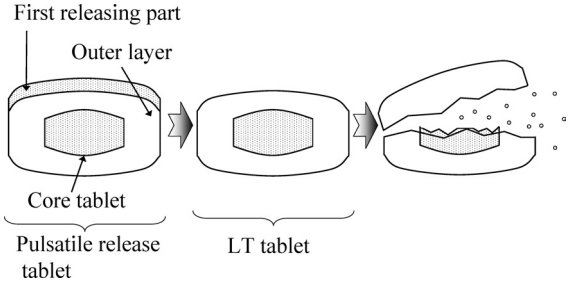

Fig. 1. Structure of Pulsatile Release Tablet and LT Tablet

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(Tokyo, Japan) Fumaric acid of food additive grade was obtained from Kawasaki Kasei Chemicals Ltd. (Japan). Calcium phosphate anhydrate, cornstarch, calcium stearate, D-mannitol, stearic acid and croscarmellose sodium were of Japanese Pharmacopoeia grade and purchased from Japanese companies. All other materials were of analytical grade.

Methods. Core Tablet Preparation The core tablets were obtained by wet granulation of filler granules containing D-mannitol, croscarmellose sodium, gelatinized cornstarch as a binder and stearic acid. The filler granules, nicorandil and calcium stearate were mixed and compressed into plain round tablets 5 mm in diameter by a single-shot tableting machine (Okada Seiko Co., Ltd. Japan). The composition of the core tablet is shown in Table 1.

LT Tablet Preparation To investigate the effect of composition of the outer layer, nine types of granules for dry coating were obtained by spray drying. The design of formulations of the outer layer is shown in Table 2. These formulations were prepared to analyze the effect of ingredients on lag time. In this view, there were two key factors for formulations to be focused on. One was content ratio of calcium phosphate anhydrate and fumaric acid which had different characteristic of wettability. Another was the content ratio of corn starch as binder which was expected affecting to water penetration through the outer layer. These two factors were varied within an available region to prepare nine formulations for multiple regression analysis. The two factors were normalized using code X_1 and X_2 shown in Table 2 to avoid some problem of weighting. The code X_1 and X_2 was defined as normalized calcium phosphate content and corn starch content respectively.

The dry-coated tablet producing machine was designed with three parts, that is, layering units, a core-supply unit to form a dry-coated tablet and fast dissolving layer simultaneously because this machine was designed for a final tablet forming process starting with rapid release followed by a second release with a lag time. The tabletting machine, model LIB20818LD1JZ, was produced by Kikusui Seisakusho Ltd. Although three layers were possible, only the dry-coated tableting function was used in this study because the objective was to evaluate formation of the lag time release from tablet and the factors that control the release lag time. The LT tablet evaluation makes it possible to simplify the factor analysis.

The LT tablet was compressed with a core tablet and 500 mg of outer layer granules into a double R round tablet 9.5 mm in diameter with a total weight of 550 mg. The tablet compression pressure was set at 29 kN per punch to obtain a LT tablet with lower lag time deviation than 20 kN compressions (Comparative compression data was shown in Table 3).

Dissolution Test The lag time of release was evaluated by the dissolution test. The test apparatus was dissolution tester NTR-VP6P (Toyama Sangyo Co., Ltd. Japan) in compliance with the Japanese Pharmacopoeia. In this study, the standard dissolution test was performed using the paddle method. The rotation speed was 50 rpm. The test solution was 500 ml purified water. The temperature of the test solution was 37 °C. At the appropriate time, the test solution was collected and the concentration of nicorandil was determined by HPLC. All the samples were tested for three times. The dissolution lag time was defined as the time when dissolution of 5% or more of nicorandil was observed.

Water Penetration Study To visualize the penetration of water in the dry coated layer, Brilliant Blue FCF was added to the test solution. The sample tablet was immersed in the dye solution for a preset period under the same conditions as the standard dissolution test. At the sampling time, the sample tablet was removed immediately from the vessel, dried and cut to observe the cross section of the tablet. The thickness of the colored outer layer was measured.

Results and Discussion

Proof of Concept of the LT Tablet Typical release profiles of LT tablets are shown in Fig. 2. All release profiles showed rapid nicorandil release from the LT tablet after the lag time. The LT tablets of Rp. 1 and Rp. 5 showed the lag times of 160 and 310 min, respectively. They also showed pulsatile release behavior after distinct lag time. Thus, this LT tablet could control the pulsatile release after lag time by only controlling the core formulation of the tablet. This result confirmed that the concept of pulsatile release can be realized using the LT tablet as a release control unit.

Outer Layer Composition and Lag Time Length From the results of dissolution test, the lag times of nine formulations were obtained as shown in Table 4. These results were analyzed by multiple regression using two codes X_1 and X_2. From the results of the analysis, The lag time was indicated as the equation as follows and simulations of some lag time by this equation were plotted on the designed space of this experiment using code X_1 and X_2 (Fig. 3).

Table 1. Composition of the Core Tablet

Ingredient	Content
Nicorandil	5.25 mg
Mannitol	36.95 mg
Stearic acid	4.00 mg
Croscarmellose sodium	2.40 mg
Corn starch	1.10 mg
Calcium stearate	0.30 mg
Total	50.00 mg

Table 3. Compression Pressure Effect on Lag Time Deviation

Pressure (kN)	Lag-time (min)		Standard deviation	
	20	29	20	29
RP1	160	180	35	0
RP3	267	267	31	23
RP5	280	310	17	17
RP9	173	207	61	12

Table 2. Composition of the Outer Layer

	Rp. 1	Rp. 2	Rp. 3	Rp. 4	Rp. 5	Rp. 6	Rp. 7	Rp. 8	Rp. 9
Content ratio in Spray dried granule									
Fumaric acid	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
$CaHPO_4$	15.00	15.00	5.00	5.00	2.93	17.07	10.00	10.00	10.00
Corn starch	1.50	0.50	1.50	0.50	1.00	1.00	0.29	1.71	1.00
Code X_1	1	1	−1	−1	−1.41	1.41	0	0	0
Code X_2	1	−1	1	−1	0	0	−1.41	1.41	0
Actual ratio (%) of outer layer									
Fumaric acid	66.55	67.75	80.86	82.64	85.59	64.75	74.76	72.72	73.73
$CaHPO_4$	24.95	25.40	10.11	10.33	6.27	27.63	18.69	18.18	18.43
Corn starch	2.5	0.85	3.03	1.03	2.14	1.62	0.55	3.1	1.84
Stearic acid	5	5	5	5	5	5	5	5	5
Calcium stearate	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100

Table 4. LT Tablet Lag Time for Various Compositions of the Outer Layer

	Rp. 1	Rp. 2	Rp. 3	Rp. 4	Rp. 5	Rp. 6	Rp. 7	Rp. 8	Rp. 9
Fumaric acid (%)	66.55	67.75	80.86	82.64	85.59	64.75	74.76	72.72	73.73
$CaHPO_4$ (%)	24.95	25.40	10.11	10.33	6.27	27.63	18.69	18.18	18.43
Corn starch (%)	2.50	0.85	3.03	1.03	2.14	1.62	0.55	3.10	1.84
Lag-time (min)	160	90	247	207	310	127	150	213	187

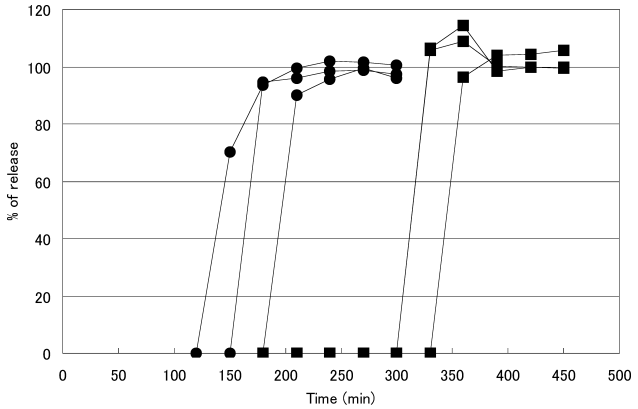

Fig. 2. Dissolution Profiles of LT Tablets Rp. 1 and Rp. 5

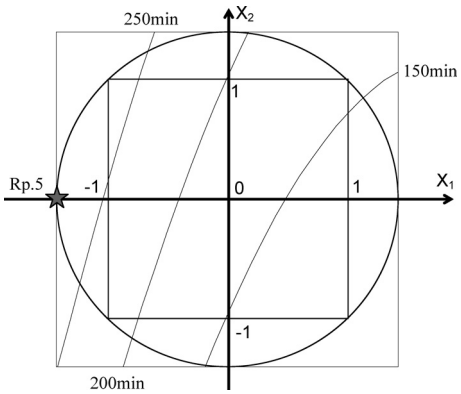

Fig. 3. Simulated Lag Time by Outer Layer Content Variation

The line indicating 150, 200, and 250 min lag time are plotted. The circle represents simulation available area.

$$\text{lag time} = 174 - 57.8X_1 + 24.8X_2 + 15.3X_1^2$$

The lag time of LT tablets showed a positive correlation with the content of fumaric acid and consequently a negative correlation with the content of calcium phosphate anhydrate *i.e.* fumaric acid prolongs the lag time of pulsatile release, however, calcium phosphate anhydrate shortens it. These results indicated that the dominant factor to determine the in lag time of pulsatile release was the formulation ratio of calcium phosphate anhydrate and fumaric acid. On the other hand, corn starch showed a weak positive correlation with lag time. Although the binding agents expected to work as a water penetration pathways due to the wettability of binding agents. However, the addition of corn starch slightly delayed the lag time. These results suggested that the corn starch swells during the penetration of water and blocks the penetration pathways. Consequently, Rp. 5 was the nearest to the point that represent the longest lag time in this simulation.

The wax matrix system is well known as sustained release dosage forms. In this formulation, stearic acid was added as lubricants to prevent the tablet material from adhering to the die wall. Although the main purpose of adding lubricants was not release modification, However, as the stearic acid was added to the formulation, the effect of stearic acid on lag time release was confirmed by the dissolution test of the LT tablets. No difference in lag time was observed between tablets with and without stearic acid. The results indicated that the addition of stearic acid did not affect on the lag time of LT tablets in this formulation. (Refer to patent[7])

These results demonstrated that fumaric acid might be the dominant ingredient for outer layer to control the lag time of pulsate release and it was assumed that fumaric acid played the most important role in the outer layer matrix to create the long lag time.

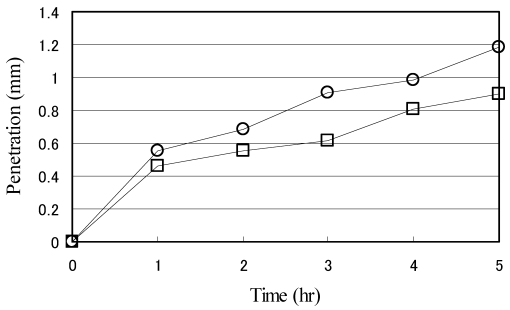

Fig. 4. Time Profiles of Water Penetration Depth

The circles and squares represent the penetration depth in the radial and perpendicular directions of the LT tablet respectively.

Penetration Rate Analysis Penetration profiles of typical samples (Rp. 5) are shown in Fig. 4. The penetration rate in the radial direction was about 30% faster than that in the perpendicular direction. This result indicted that the lag time was mainly determined by the water penetration in the radial direction of tablet. Thus, rate analysis should be focused on the penetration of water into the radial direction of tablet.

In general, it is well known that solvent penetration into a powder layer is represented as the penetration of a liquid into cylindrical capillaries as shown in Washburn's Eq. 1. Where h is the penetration depth of the liquid, t is the time from contact of the liquid and powder, r is the mean radius of the capillary tube in the powder layer, γ_L is the surface tension of the liquid, θ is the contact angle and η is the viscosity of the liquid.[8]

$$h^2 = \frac{r\gamma_L \cos\theta}{2\eta} \cdot t \quad (1)$$

This equation can be converted into Eq. 2. In this study, parameters except for t and h can be considered as constants. The Eq. 2 can be simplified as Eq. 3, where C is a constant.

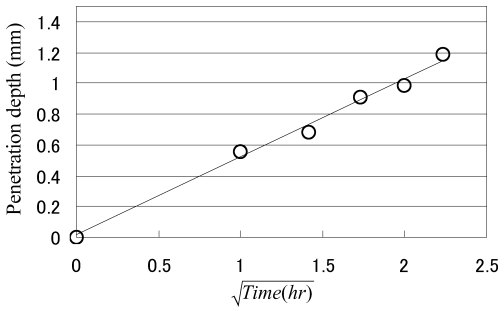

Fig. 5. Relationship between Penetration Depth and Square Root of Time
The circles represent data points and the line represents regression.

$$h = \sqrt{\frac{tr\gamma_L \cos\theta}{2\eta}} \tag{2}$$

$$h = C\sqrt{t} \tag{3}$$

From Eq. 3, based on Washburn's equation, the penetration depth is directly proportional to the square root of time. The water penetration depth in the radial direction was appropriately measured and plotted against the square root of the time as shown in Fig. 5.

The water penetration depth in the radial direction was closely correlated with the square root of time. This suggested that the penetration depth of water follows Washburn's equation, then the mechanism of the water penetration could be treated as a simple water penetration model. So, the pulsatile release of nicorandil was occurred just when water penetration reached the core tablet, and the water penetration time through the outer layer might determined the lag time of pulsatile release. In addition, visual observation results supported this simple water penetration mechanism that was independent from erosion of the LT tablet itself, because the shape of LT tablet had been kept the shape of tablet until the pulsatile release.

Then, the lag time T can be expressed as Eq. 4 by replacing parameter h with Δd, where Δd is the diameter difference between the core tablet and LT tablet.

$$T = \frac{\eta \Delta d^2}{8r\gamma_L \cos\theta} \tag{4}$$

This equation suggested that Δd is a sensitive parameter related to LT tablet production. This parameter can be adjusted by changing the diameter of the core tablet or LT tablet. Consequently, this equation suggested that the critical parameter for industrial production is the consistency of the lag time by maintaining the accuracy of centering of the core tablet.

Conclusion

A dry coated LT tablet was designed to perform the pulsatile release of nicorandil with the accurate lag time. The lag time of the LT tablet was controlled by adjusting the composition of formulation and the thickness of the outer layer. A water penetration study demonstrated that the mechanism of lag time was due to the simple penetration of water through the outer layer and the lag time could be explained by Washburn's equation.

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