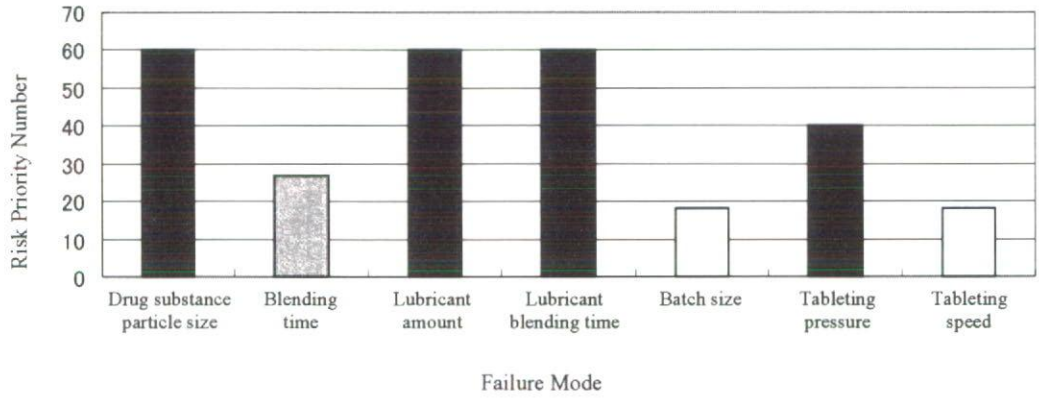


Figure 2.3.P.2.3-1 Results of FMEA Risk Analysis on Drug Product Composition and Manufacturing Process of Sakura Tablet

2) Effect of Critical Process Parameter on Drug Product Quality

2)-1 Evaluation Methods

For evaluation of effect of each critical process parameter on the drug product quality, conditions for dissolution test were investigated. The condition should detect the influences on dissolution from tablets with varied drug substance partcle size, lubrication condition and compression force, and correlates with in vivo performance in human.

2)-1-1 Development of Dissolution Test Method

Dissolution profile of tablets with varied drug substance partcle size, lubricant amount and compression force manufactured in a small scale or a pilot plant scale was measured using dissolution test method with a medium of 0.1% sodium lauryl sulphate aqueous solution. As shown in Figure 2.3.P.2.3-2, the dissolution test method had discrimination capability of drug product properties. Composing of the large particle size API made the dissolution rate particularly slow. Based on these results, it was confirmed that the dissolution test method had discrimination capability of manufactured tablets with varied manufacturing parameters.

Details of the dissolution test method are shown in Section 2.3.P.5.2 Test Methods (Analytical Procedure) and Section 2.3.P.5.3 Validation of Test Methods (Analytical Procedure).

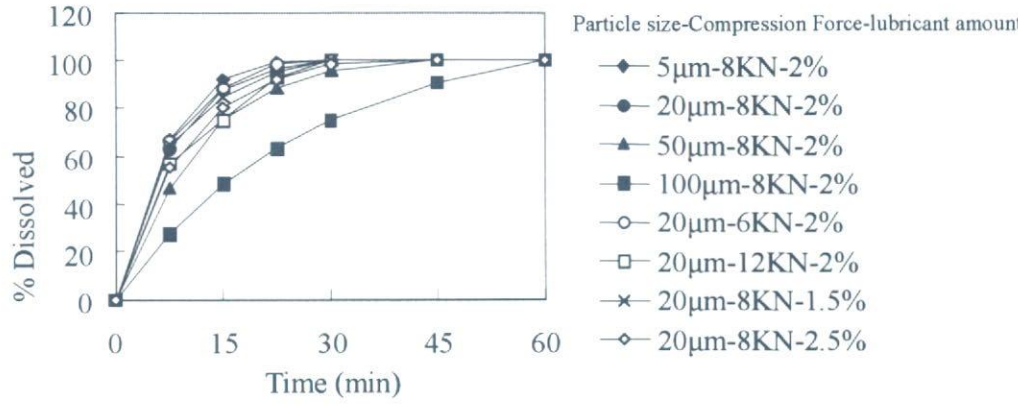


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Particle Size (D90%), Compression Force and/or Lubricant Amount

2)-1-2 In vivo Evaluation

Following the confirmation in the above 2)-1-1, in vivo blood concentration profiles of the API after administered tablets manufactured in a pilot plant scale with composing different particle sizes are investigated. As shown in Figure 2.3.P.2.3-3, a trend that larger particle sizes of API correlated with lower Cmax, and slightly longer Tmax was observed. In particular, in the case of drug substance particle sizes of 100 μm, significantly lower Cmax and AUC were obtained, compared to ≤50μm particle size. In Section 2.5.2 Overview of Biopharmaceutics, details of this study were shown.

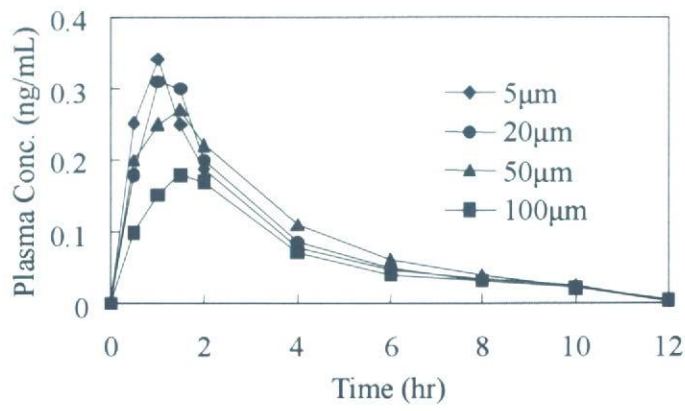


Figure 2.3.P.2.3-3 Blood Concentration Profiles

2)-1-3 IVIVC (in vitro/in vivo Correlation)

Based on the results of in vitro dissolution profiles shown in 2)-1-1 Development of Dissolution Test Method and in vivo blood concentration profiles shown in 2)-1-2 In vivo Evaluation, the established dissolution test method showed discrimination capability of tablets manufactured with the varied parameters, and the IVIVC was confirmed. Therefore, it was concluded that this dissolution test method may be applied to evaluate quality of the tablet manufactured within a design space.

2)-2 Effect of drug substance partcle size

As shown in 2.3.P.2.3-2, dissolution rate became slow when an API with 100 μm particle size (D90) was composed, however when the size was within the range of 5 to 50 μm, dissolution profiles were the same. Moreover, as shown in 1)-1-2 In vivo test, when a tablet comosed API of 100 μm particle size was orally administered, lower Cmax and AUC were observed, although high bioavailability was observed by composing a API of ≤50μm particle size.

As described in 2.3.P.2.2 3) Initial Risk Assessment (Design Risk Assessment), due to the low solubility and high permeability of API, the particle size of API affects its dissolution from tablets and in vivo pharmacokinetics. However, dissolution properties and in vivo absorption were same over the particle size range of 5 to 50 μm.

2)-3 Effect of Conditions of Lubrication Process

At 3 levels each of lubricant amount and lubricant blending time, the tablets were manufactured, and the effects on dissolution profile and hardness of tablets were evaluated. The results indicated that tablets manufactured in all conditions showed the similar dissolution profiles, and increase of lubricant amount and blending time tended to decrease tablet hardness (Figure 2.3.P.2.3-4). However the hardness in the study range highly exceeded the in-process control lower limit, 80N, therefore it was confirmed that these parameters did not affect the dissolution or tablet hardness significantly, and the lubricant amount of 2% was justified.

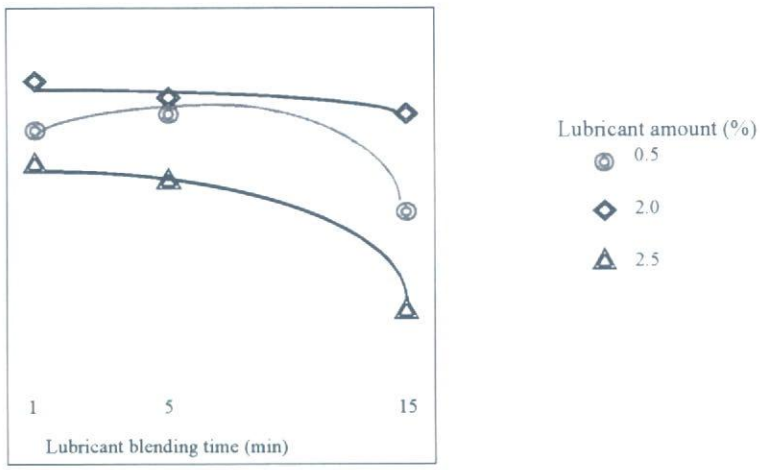


Figure 2.3.P.2.3-4 Correlation between Lubricant Amount, Lubrication Time and Tablet Hardness

2)-4 Effect of Tableting Process

Effects of content uniformity, hardness, dissolution, and friability of tablet were investigated by manufactured with various tableting process parameters. Although the tablet hardness and friability tended to decrease slightly when compression force was low, the target product properties were achieved. On the other hand, when compression force was high, the dissolved amount at earlier testing time tended to be low, and it was difficult to achieve ≥80% dissolution in 30 minutes. Regarding rotation speed of tableting machine, when rotation speed increased the acceptance value of content uniformity tended to increase, however all values met the criterion of ≤15.0%.

From these results, the mean weight of the tablets and compression force (6 to 10KN) were employed in the process control.

Table 2.3.P.2.3-2 Test Results of Tableting Process Parameters

Tableting condition			Tablet properties			
Rotation speed of tableting machine	Rotation speed of force feeder	Compression force KN	Content Uniformity	Dissolution (%) at 15 minutes	Hardness (N)	Tablet strength (F intensity, friability (%)
40 rpm	40 rpm	6	2.2	97	90	0.5
		8	1.9	95	109	0.3
		10	1.7	85	131	0.1
		12	2.4	75	159	0.1
80 rpm	60 rpm	6	3.6	97	81	0.6
		8	3.7	97	104	0.4
		10	3.1	86	123	0.1
		12	3.8	73	141	0.1

2)-5 Confirmation of Critical Factors and Interactions

Results shown above indicate that the drug substance particle size affects dissolution, the lubrication condition affects tablet hardness, and the compression force affects both. However, it was confirmed that similar dissolution profiles were achieved with the range of drug substance partcle size from 5 to 50 μm, and the target product profile was obtained with the ranges of compression force and lubrication time of 6 to 10 KN and 1 to 15 minutes, respectively. Tablets were then manufactured at the levels of factors which cover all the evaluated levels to assess robustness of the manufacturing process. In the method, all factors were allocated in a $L_9(3^4)$ orthogonal arrays table to assess the effects of these parameters on interactions, drug product properties, and manufacturing efficiency. For each value of drug product property, multiple regression analyses were performed, and contribution ratio and statistical significance were confirmed for each property. The results showed no interactions among the parameters.

Table 2.3.P.2.3-1 Experimental Design of $L_9(3^4)$ Orthogonal Arrays Allocation

Parameters / No.	Drug substance particle size (μm)	Lubricant amount (%)	Lubrication time (min)	Compression Force (KN)
1	5	1.5	1	8
2	5	2	5	10
3	5	2.5	15	12
4	20	1.5	5	12
5	20	2	15	8
6	20	2.5	1	10
7	50	1.5	15	10
8	50	2	1	12
9	50	2.5	5	8

3) Effects of Other Process Parameters on Tablet Quality

3)-1 Effects of Blending Process on Homogeneity

In the initial risk assessment, Sakura Tablet could not be manufactured by wet-granulation due to the susceptibility to hydrolysis, therefore the direct compression method was adopted. Blending conditions such as blending time and rotation speed and drug substance partcle size are expected to affect content uniformity. Therefore, an experiment on a small scale according to an experimental design was performed to obtain information of effects of parameter variations on the homogeneity of the blended powder, although the risk has been judged as medium in the risk assessment. Homogeneity of the blended powder samples was assessed using an in-line near infrared spectrophotometry (hereafter referred to as NIR), as well as a high performance liquid chromatography (HPLC).

The study results showed robustness of blending process against a large variation of process parameters. On the other hand, when variations of factors occurred simultaneously (drug substance particle size was large, V type blender was used, blending time was short, blending rate was slow), relative standard deviation of blending homogeneity was 6.5%, which indicated a trend of larger variations.

As a result, the manufacturing of tablets with the target content uniformity was confirmed, even if each parameter of drug substance partcle size, type of blender and blending speed were varied in the studied experimental range, the blending was stopped at the time when relative standard deviation of blending homogeneity was <6%.

In 3.2.P.3.3 Manufacturing Process and Process Control, the NIR monitoring system was described.

Variation factor:

- Time: from 2 to 16 minutes
- Blending speed: 10 to 30 rpm
- Equipment: Drum type and V type blender
- Drug substance particle size: D90 = 10 to 50 μm

Table 2.3.P.2.3-1 Experimental Design for Blending Process Parameter Assessment

Experiment No.	Run	Condition	Blending time (minutes)	Rotation speed (rpm)	Blender	Particle size D90 (μm)
1	2	varied	2	10	V type	10
2	7	varied	16	10	V type	50
3	10	varied	2	30	V type	50
4	5	varied	16	30	V type	10
5	6	varied	2	10	Drum type	50
6	1	varied	16	10	Drum type	10
7	8	varied	2	30	Drum type	10
8	11	varied	16	30	Drum type	50
9	3	standard	9	20	V type	30
10	12	standard	9	20	Drum type	30
11	9	standard	9	20	V type	30
12	4	standard	9	20	Drum type	30

Note) Content Uniformity results in the above experiments must be presented.

4) Effect of Manufacturing Process on Quality

As for the main parameters identified in the evaluation of the manufacturing process, effects on the tablet quality were evaluated, and the results were summarized in Figure 2.3.P.2.3-5. The figure shows that drug substance particle size may highly affect dissolution, and also tableting pressure may highly affect tablet hardness. However, as shown in 2)-4 Effect of Tableting Process, manufacturing of the drug product with the target quality over the range of tableting pressure from 6 to 10 KN was confirmed.

	Clinical quality			Physical quality	
	Disolution	Assay	Content uniformity	Appearance	Hardness
Material characteristics					
Drug substance partcle size					
Lubricant amount on tablet surface					
Process parameters					
Blending (speed and time)					
Lubricant (blending speed and time)					
Tableting pressure					
Tableting speed					
Batch size					

- Low risk
- Medium risk
- High risk

Figure 2.3.P.2.3-5 Summary of Effects of Each Parameter on Tablet Quality

5) Risk Assessment after Manufacturing Process Development

FMEA risk assessment was performed for the drug product manufactured by the planned commercial scale and manufacturing processes which may fully affect the tablet quality. As shown in Figure 2.3.P.2.3-6, drug substance particle size most affected the final product quality. Risk scores became low on lubricant amount and tableting pressure, which were identified as critical quality properties in the risk assessment before establishment of the commercial scale, because as shown in 2)-1-1 Dissolution, variation of lubricant amount and tableting pressure did not change the dissolution of tablets which were manufactured in a pilot plant scale indicating small effects on final product quality.

The blending process and tableting process, which include failure mode judged as medium risk in the risk assessment after manufacturing process development, were judged as critical processes.

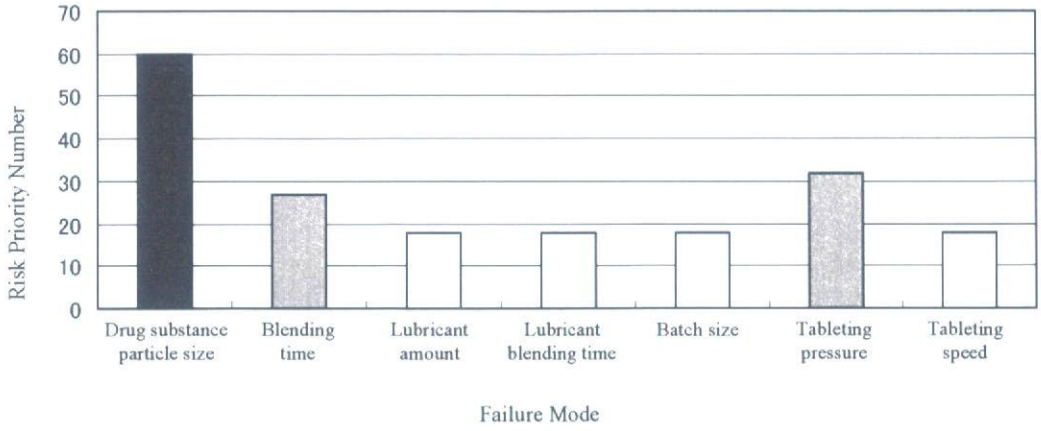


Figure 2.3.P.2.3-6 Results of FMEA Risk Assessment after Manufacturing Process Development for Sakura Tablet

6) Evaluation and Construction of Design Space as Control Strategy

6)-1 Evaluation of Control Strategy of Quality Properties

Control strategy was evaluated for dissolution, content uniformity and assay, which are indexes of quality property for clinical studies.

6)-1-1 Dissolution

Effects of drug substance particle size, lubricant amount, lubricant blending time and tableting pressure on dissolution were clarified using a multidimensional analysis. During manufacturing process development, effects of blending process, lubricant blending process and tableting process on dissolution were small and effects of drug substance particle size were largest for dissolution. Therefore, the drug substance particle size was controlled as an input variable in the design space.

6)-1-2 Content Uniformity

In 3)-1 Effects of blending process on homogeneity, influences of the input variable (drug substance particle size) and blending process on process parameters (blending time, rotation speed and blending machine) were studied, and its effects on content uniformity were clarified. Based on the understanding of the blending process during the study, it was considered that two control strategies of different combinations of controlled items as shown in Figure 2.3.P.2.3-7 were feasible. In case of control strategy 1, many parameters depending on the equipment and scale are included. Therefore, control strategy 2 was chosen because the final drug product met the criterion of the content uniformity test by confirmation of

blend homogeneity (relative standard deviation <6%) and control of the end point by the in-line NIR, and the real time release was employed.

In the case of NIR use, it was confirmed that control of blending end point did not depend on manufacturing scale or equipment.

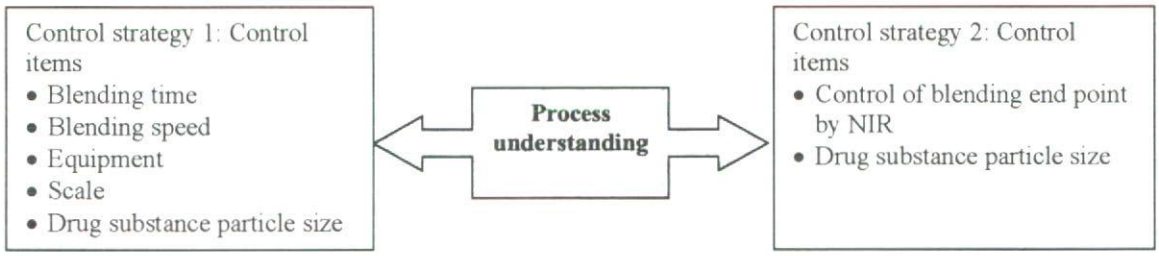


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

Note) In the case of employment of control strategy 1, it is possible that drug substance partcle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.

6)-1-3 Assay

Effects of the input variable (drug substance particle size) and the process parameters (blending, lubricant blending process and tableting pressure, etc.) on assay values were clarified using a multidimensional analysis. From the results it was judged that there were no effects of input variables or process parameters on assay values. Therefore, an assay specification was set, and mean weight of the tablet was controlled in the control strategy.

6)-2 Design Space Construction

The design space of Sakura Tablet was constructed by a combination of the process input (input variable and process parameters) and specification of the final product, based on the control strategy of the quality properties as described above.

6)-2-1 Input Variable

Drug substance particle size was chosen as an input variable in the design space construction because this parameter most affected dissolution, and target dissolution was obtained by controlling the particle in the size range of 5 to 20 μm.

6)-2-2 Process Parameter

During manufacturing process development, it was revealed that blending process, lubricant blending process and tableting process give small impact on clinical quality. These processes were included as a component in the design space because it has been demonstrated that drug product with appropriate quality can be manufactured when applying the controls shown below.

6)-2-2-1 Blending Process

Control of relative standard deviation of blending homogeneity <6% using the NIR was included in the design space because, based on confirmation of the blending homogeneity and control of the end point using the in-line NIR, appropriate content uniformity of the final drug product was available not depending on equipment or manufacturing scale.

6)-2-2-2 Lubricant Blending Process

The design space of the lubricant blending time will be established after process validation at the commercial scale production,although it was confirmed on a small scale that the lubricant amount of 2% was justified and blending time of from 1 to 15 minutes did not affect the dissolution or hardness of the tablets remarkably.

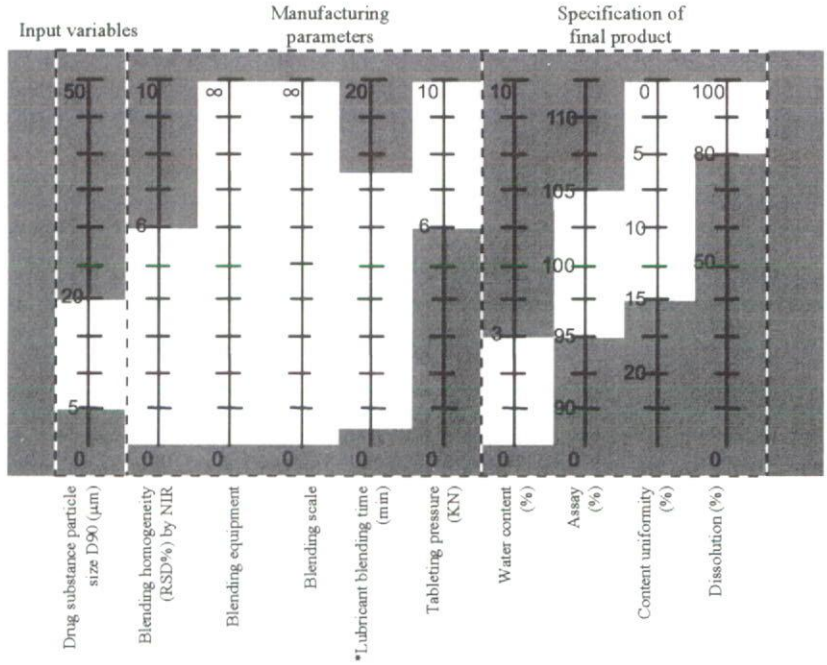
6)-2-2 Tableting Process

Tableting pressure 6 to 10 KN has been demonstrated to produce tablets with appropriate quality, therefore this pressure range was set in the design space.

6)-3 Final Product Specification

Water content was set as a component in the design space to control assay, content uniformity, dissolution, and generation of impurities produced from hydrolysis of the API which were identified, in the target profiles, as specification items for the final drug product to assure safety and efficacy during the shelf-life. Each specification is shown in Section 2.3.P.5.6 Justification of specification and test methods.

The design space using a parallel coordinate axis method was constructed because there were no interactions between components in the design space described above. The design space was shown in Figure 2.3.P.2.3-8.



*: Design space will be established after process validation in the commercial scale

Figure 2.3.P.2.3-8 Design Space of Sakura Tablet

7) Release Strategy of Final Drug Product

(1) Dissolution

For the drug substance particle size and the tableting pressure which affected tablet quality as shown in Figure 2.3.P.2.3-6, a multidimensional calculation method was established to assess correlation with dissolution rate, and this method was used in validation of the first commercial tablet.

Dissolution rate is set in the Specification and Test Methods, however the test is not performed at the release of the commercial product because this calculation method assures specification conformity of dissolution rate.

(2) Content Uniformity

In the blending process, a validated in-line NIR monitoring system was employed. Therefore, for control of the blending process a feed back loop was used, and not end point control at a certain time point.

Content uniformity of tablets is assured by confirming the blending homogeneity by NIR prior to the lubricant blending process.

In the tableting process, Content uniformity was assured by using PCD equipment which monitors tableting pressure of each tablet and excludes tablets in which the pressure is out of the control range as

critical abnormality, and by using WAC equipment which performs feedback control of PCD equipment by mean weight of tablets which are sampled automatically.

Description on the in-line NIR monitoring system used in the blending process is presented in Section 3.2.P.3.3 Manufacturing process and process control.

In Specification and Test Methods, drug product homogeneity (content uniformity) is set, however it is not tested at release of the tablet because monitoring of the blending homogeneity in the blending process and tableting pressure in the tableting process can assure the content uniformity of tablets.

(3) Content (Assay)

In Specification and Test Methods, the assay is set, however it is not tested at the release of the tablet because content of the blended powder in the blending process and mean weight of tablets after tableting can assure the content of the active ingredient.

The description on determination method of tablet weight after the tableting process is presented in Section 3.2.P.3.3 Manufacturing Process and Process Control.

When a new manufacturing line is introduced, application of controlling methods in each manufacturing process will be reconfirmed. Until the introduction content uniformity*, dissolution test* and content (assay)* will be applied as shown in Section 2.3.P.5.1 Specification and Test Methods. Also, for yearly stability tests, dissolution test* and content (assay)* will be applied.

8) Risk Assessment after Control Strategy Implementation

Results of the risk analysis using control strategy FMEA are shown in Figure 2.3.P.2.3-9. The results may indicate that appropriate control of parameters, which affects the tablet quality, can be attained.

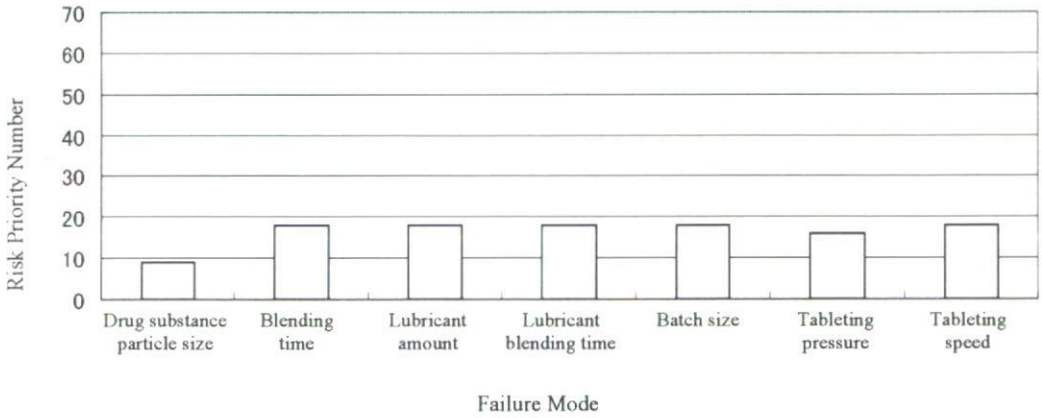


Figure 2.3.P.2.3-9 Results of FMEA Risk Analysis for Sakura Tablet after Control Strategy Implementation

2.3.P.2.4 Container Closure System

In a stability test, tablets adsorbed water at a maximum by 3% under the condition of ≥75%RH.

Afterwards, by a packaging/vapour permeation test, it was confirmed that polypropylene blister packaging could control water adsorption in ≤3%.

From the results of the stability study and evaluation of the design space, it was confirmed that Sakura Tablet manufactured in the range of the design space and packed in the polypropylene blister were stable for not less than 24 months at 25°C.

2.3.P.2.5 Microbiological Attributes

Microbial limit testing was set. However, the testing by each release test is not considered necessary because of the following reasons.

- Amokinol has no action to promote microbial growth.
- Water and excipients used in drug product manufacturing meet JP.
- At the release of Sakura Tablet by 10 lots, Microbial Limit Test JP is performed.
- Stability testing is performed and monitored with 1 lot every year.

2.3.P.2.6 Compatibility

Not applicable because the final product is a tablet.

2.3.P.3 Manufacture

2.3.P.3.3 Manufacturing Process and Process Control

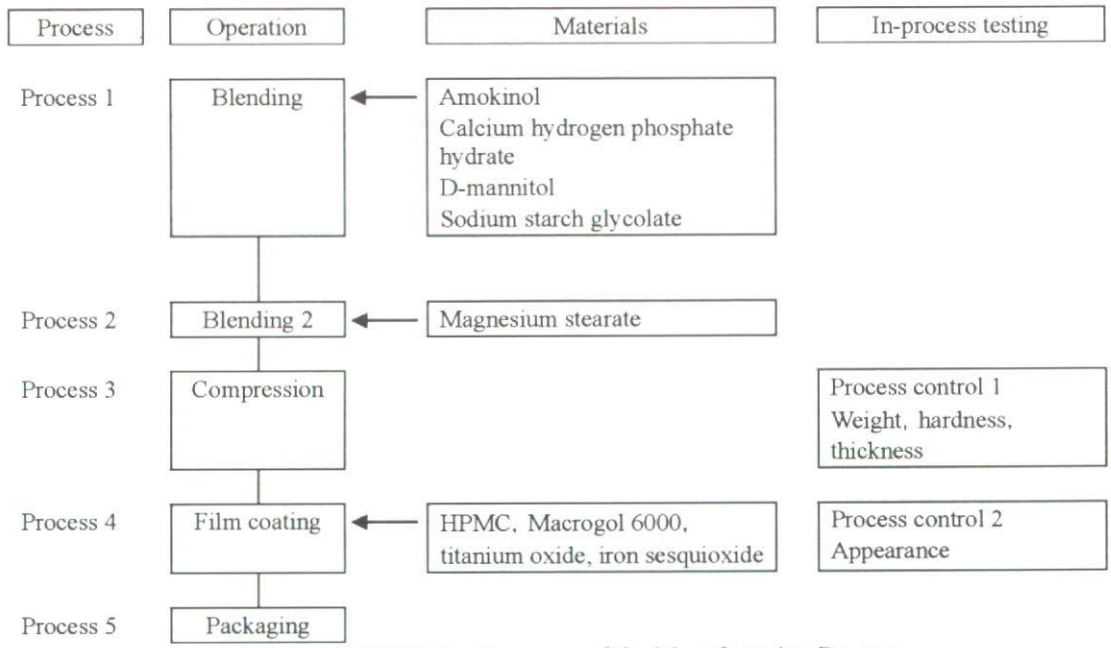


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

2.3.P.3.3.1 Manufacturing Parameters and Specifications

Table 2.3.P.3.3-1 Manufacturing Parameter for Each Process

Drug substance	Particle size	
Magnesium stearate	Specific surface area	
Blending process	Blending speed	XX rpm
	Blending time	Stop at the time point when the set standard of homogeneity is met.
Lubricant	Blending time	XX ± X minutes
Compression process	Filling speed	XXX
	Compression pressure	XX KN
	Tablet weight	XXX ± X mg

2.3.P.3.3.2. Control Method

A design space was constructed with the blending process, based on an understanding of the manufacturing process in Section 2.3.P.2.2.3. The controls and tablet weight were monitored after compression was performed to manufacture the tablets in the design space.

Real-time release was employed, based on the results of developing the drug product as shown in Table 2.3.P.3.3.2, considering that multiple forms of control can each serve as a test of the specifications to maintain tablet quality.

Table 2.3.P.3.3.-2 Specifications, Monitored Process and Variables impacting on Quality Properties

Specifications and test methods	Process	Quality property
Dissolution test	Drug substance	Drug substance particle size
	Material	Specific surface area of magnesium stearate
	Blending	Lubricant blending time
	Compression	Compression pressure
Content uniformity	Blending	Blending homogeneity of the drug substance
	Compression	Weight deviation
Content (assay)	Blending	Content of blended powder
	Compression	Tablet weight

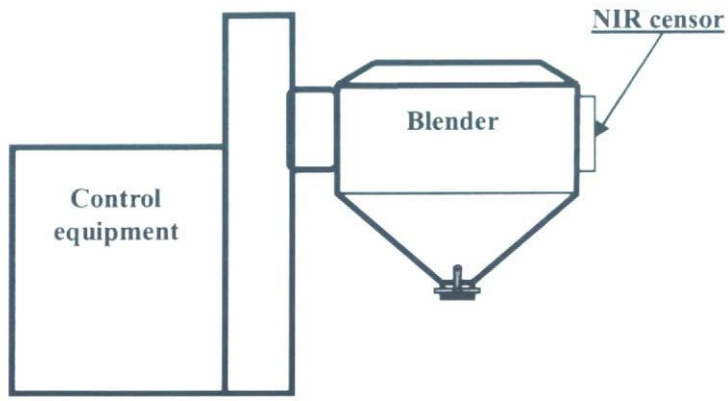
2.3.P.3.3.3 Monitoring of Quality Properties

For the real-time release of content uniformity, monitoring of homogeneity by the in-line NIR at blending process and monitoring of the drug product weight calculated by tablet weight at compression process were employed. Monitoring methods used in each process are described below.
To achieve real-time release of the assay, blended powder assay was measured within the blending process, and 20 samples were taken for weight measurement of 10 tablets per each sampling point during compression process.

2.3.P.3.3.3.1 Blending Process

The in-line NIR method was employed for monitoring the blending process, as this method gives real time analysis of the progress of the blending process as opposed to off line testing by the HPLC method in monitoring the homogeneity of the active ingredients in the blending process. The determination conditions of the in-line NIR method were assessed by evaluating the position of the sensor and the determination conditions, and the conditions were set as below:

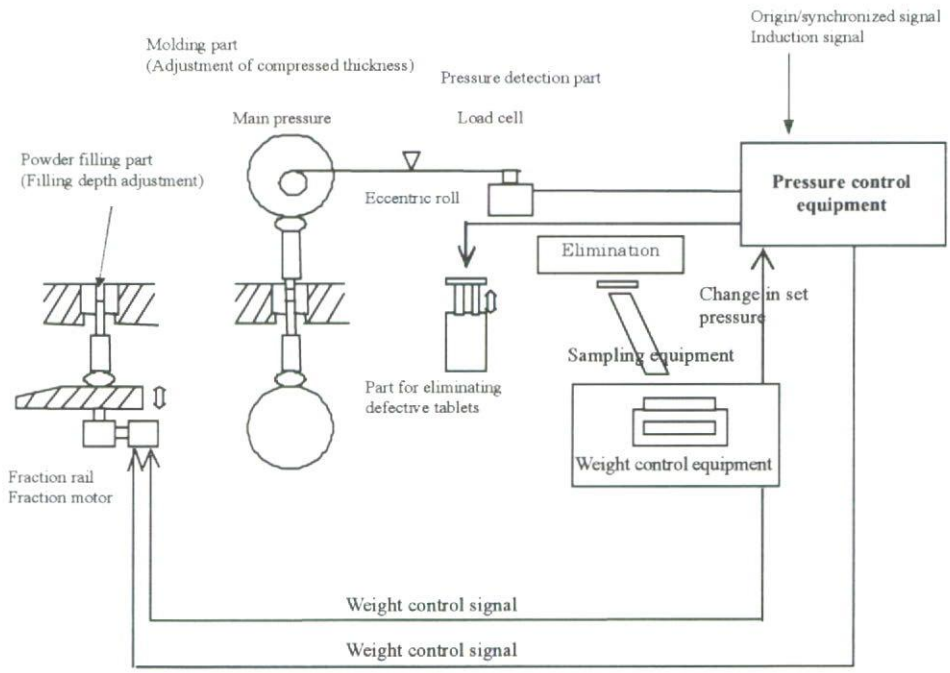
Equipment: XXXXX
Location of censor attachment: Side position of the blender
Wavelength: XXXX cm^{-1} (Range of wave number: XXX to XXX cm^{-1})
Spectral Acquisition mode: diffuse reflectance



2.3.P.3.3.2.3. Compression Process

Online monitoring control was employed for the compression pressure of each tablet in the compression process. Based on information concerning the compression pressure, the amounts of filled blended powder (filling depth) were adjusted and the tablets that were off-specification were eliminated by the compression pressure control equipment. In addition, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression pressure control equipment was also selected by feeding back the mean weight information of regularly and automatically sampled tablets.

Balance: XXXXX
Equipment for measuring the compression pressure: XXXXX
Equipment for conducting automatic sample measurements/equipment for controlling weight: XXXX



2.3.P.3.4 Control of Critical Process and Critical Intermediates

Among the specification test items, real-time release was employed for the content uniformity test, dissolution test and content (assay). The process control methods that serve as each test method are as shown below.

2.3.P.3.4.1 Test Items in Real-time Release

Based on the control strategy described in Section 2.3.P.2.3 Manufacturing Process, the dissolution test, content uniformity test and content were judged as candidates for real-time release.

2.3.P.3.4.1.1 Content Uniformity Test

To ensure content uniformity in the final product, the homogeneity of the blended powder in the blending process and compression pressure in the compression process were monitored for control.

The authors employed a control method whereby homogeneity was monitored in the blending process by the in-line NIR that finished the blending process when the values of ten continuous samples were within the acceptable range shown in Table 2.3.P.3.4.1-1.

Based on evaluation of blended powder using HPLC method at pilot plant scale, and result obtained from assay homogeneity following compression, it was confirmed that assay homogeneity for tablet can always be managed to fall within acceptance criteria when blending homogeneity is monitored within inline NIR during blending process.

Table 2.3.P.3.4.1.1-1 Acceptable Range of the Homogeneity of Blended Powder

Number of points sampled	n = 10
Acceptable range	Mean = within 2% of the labeled value
	RSD: 1.0% or less

Compression pressure in the compression process was controlled using Auto Weight Control (AWC). AWC is a control method that utilizes the linear relationship between the compression pressure and the weight of the drug product. The weight of the tablet is calculated from the determined compression pressure. Tablets not meeting the specified criteria are rejected. The application of this system makes it possible to control the compression pressure of all tablets. The combination of this method with control of the homogeneity of the blended powder is believed to control content uniformity of the drug product. Therefore, it was decided that the content uniformity test could be omitted from the specifications.

Table 2.3.P.3.4.1.1-2 Control of Compression Pressure

Control range (on a weight basis)	97 to 103 mg
RSD	1.0% or less

2.3.P.3.4.1.2 Dissolution Test

The effects of each factor on the dissolution rate were studied for the drug products manufactured according to the allocation of the drug substance particle size, specific surface of magnesium stearates, lubricant blending time and compression pressure as factors. The test results were subjected to multidimensional analysis. For the formula for the sum of each factor which is multiplied by a coefficient, the coefficients that make the residual sum of squares minimum were calculated (the formula is shown below).

Dissolution (%) = 108.9 - 11.96 ×$\log_{10}$(d(0.9)) drug substance particle size - 7.556 × 10^{-5} × specific surface area of magnesium stearate - 0.1849 × lubricant blending time - 3.783×10^{-2} × compression pressure

For the particle size of the drug substance, the volume distribution was measured using a dry method without preparing the sample using a laser diffraction scattering method. For the specific surface area of magnesium stearate, nitrogen molecules were adsorbed on a surface of powder particles at low temperature, and the specific surface area was determined from the adsorption amount (BET method). The items and ranges for process control that applies to the dissolution test are shown in Table 2.3.P.3.4.1.2. By controlling each process using this system, dissolution of the drug product is believed to be controllable. Therefore, dissolution test in the specification could be omitted.

Table 2.3.P.3.4.1.2-1 Process Control Items and Control Range

Process control items	Control range
Drug substance particle size	XX-XX $\log_{10}$(d(0.9))
Specific surface area of magnesium stearate	XX-XX cm2/g
Lubricant blending time	XX-XX min
Compression pressure	XX-XX N

2.3.P.3.4.1.3 Content

For assay of the active ingredient, process control by HPLC has been set in the blending process. In the pilot scale, the weight of each ten tablets from 20 sampling points were determined over the manufacturing process. The process control ranges from these test are shown in Table 2.3.P.3.4.1.3-1. Utilizing above strategies, conclusion was drawn for this particular drug product that conventional assay studies required as part of release test can be abbreviated and used for release assessment by utilizing the assay value (refer to following calculation) that will be calculated using active ingredient assay amount in blended powder obtained during blending process, drug product weight following compression process and correction value to be taken from theoretical weight.

Content (%) = Blended powder content × drug product weight ÷ theoretical tablet weight

Table 2.3.P.3.4.1.3-1 Process Control Items and Control Range

Process control items	Control range
Content of blended powder (blending process)	98 to 102%
Tablet weight (compression process)	97 to 103 mg

2.3.P.3.4.2. Validation of Test Methods (Analytical Procedures)

For the NIR monitoring method used in the blending homogeneity test, the calibration model was constructed and validated.

[1] Construction of Calibration Model

During the blending process, sampling was performed five times at ten time points per blending

process cycle. The sampling procedure was replicated three times with materials of different particle size. The 150 samples obtained were used to construct a calibration curve. For the observed values, the HPLC method was used. It was confirmed that the observed values of the samples were in the range of ±10% of their theoretical values.

A fiber probe was used in the NIR measurement. Y software of XX Company was used to construct the calibration curves. For analysis, the method of Partial Least Squares (PLS) was used and optimization calculation was performed.

The optimized results are shown in Table 2.3.P.3.4.2-1.

Table 2.3.P.3.4.2-1 Test Results of the Calibration Curves

Items	Results
Range of wavelength for the analysis	6100 - 5500 cm^{-1}
Pre-treatment for spectrum measurement	MSC
PLS component number	5
Multiple correlation coefficient	0.985
RMSECV (standard deviation)	0.67

It was confirmed that the loading spectra used in the calibration model were similar to the spectra of the drug substance, so this model was justified.

[2] Test of the Calibration Model (Validation)

Fifty samples were tested in the validation. The validation results with samples that were sampled in the same manner as in the calibration exhibited good results, as shown in Table 2.3.P.3.4.2-2.

Table 2.3.P.3.4.2-2 Test Results of Calibration Curves

Items	Results
Multiple correlation coefficient	0.981
RMSEP (standard error)	0.75