uniformity of powder blend in blending process and compression force in tableting process, However, when a new manufacturing line will be introduced in the future, current application of each manufacturing process control methods will be re-evaluated. Until the completeion of their reevaluation, content uniformity, dissolution test and assay will be carried out at the final finished products

The results of analyses of manufacturing process output made possible to identify all the parameters to be controlled. Additionally, it was confirmed that each parameter was independent from manufacturing scale. Therefore, it was concluded that a change of manufacturing scale could be achieved by only controlling those parameters.

2) Target Product Profile

Product profiles targeted in drug product development are shown in Table 2.3.P.2.2-1.

Table 2.3.P.2.2-1 Target Product Profile of Sakura Tablet

Strength and dosage form	Immediate release tablet containing 30 mg of active ingredient.
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution.
Description and hardness	Robust tablet able to withstand transport and handling.
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance. Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm.

3) Intial Risk Assessment

Regarding physicochemical properties shown in Section 2.3.S.1.3 General Properties, initial risk assessment on Sakura Tablet quality was performed. Results are summarized in Table 2.3.P.2.2-2, and shown in Figure 2.3.P.2.2-1.

In an initial risk assessment prior to formulation development, drug substance partcle size, excipients and water content were identified as possible process inputs which could affect the tablet quality.

Table 2.3.P.2.2-2 Initial risk assessment of Sakura Tablet

Factor	Risk assessment
API	Drug substance partcle size could affect in vivo performance due to the low solubility and high permeability.
Excipient	Insoluble (inorganic) excipients could affect dissolution rate.
	Soluble (organic) excipients could affect compressing property in compression.
	Hydrophobic excipients (lubricants) could affects dissolution rate.
Manufacturing process	API is known to undergo hydrolysis and this will probably preclude aqueous wet granulation processes.
	The blending process must ensure homogenous distribution of the API to achieve the desired content uniformity. Overblending should be avoided.
	Overblending of the lubricant increases surface hydrophobicity, and may decreases dissolution rate.
	Uniformity must be controlled in the blending process.
	Excessive compaction force could increase disintegration time and thereby reduce dissolution rate.

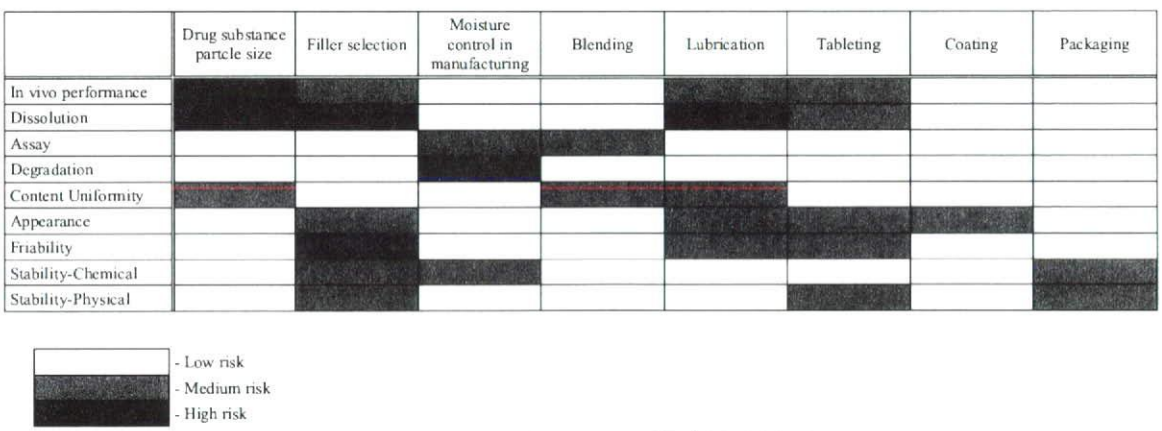


Figure 2.3.P.2.2-1 Summary of Initial Risk Assessment

2.3.P.2.2.1 Formulation Development

A direct compression process was selected as it was known that API undergoes hydrolysis and the relatively high drug loading would enable content uniformity to be achieved without a dry granulation process.

A series of soluble and insoluble fillers were screened for chemical compatibility and lactose was excluded. A dual filler system was proposed to achieve the right balance of brittle compression properties and solubility of the excipients.

In an early experimental design, calcium hydrogen phosphate hydrate and D-mannitol as filler and sodium starch glycolate as disintegrant, and magnesium stearate as lubricant were selected for the

assessment. Specific Surface Area (SSA) of magnesium stearate should be measured as a control of raw material because there is a possibility to affect on dissolution of drug product.

After selection of the above excipients, the quality of manufactured tablets were evaluated, varying the amount of the excipienet at 2 to 3 levels in the experimental design. From the results, the composition shown in Table 2.3.P.1-1 was selected.

The tablet hardness not less than 80N was chosen, and dissolution, appearance (friability, chip, etc.), content uniformity and stability as quality sttributes were assessed to judge appropriateness of tablet.

Film-coating was employed to mask the bitter taste of the API.

It is judged that the risk of control of excipienets and water, which were considered as possible critical parameters, can be prevented by the drug product design.

Note) In addition to the above description, composition changes and bioequivalence of the drug products used in clinical development must be described.

2.3.P.2.2.2 Overages (Sakura Tablet, Film-coated Tablet)

Not applicable

2.3.P.2.2.3 Physicochemical and Biological Properties

Solubility of the active ingredient, amokinol, is low and its permeability was high. Therefore, a better absorption from gastrointestinal tract can be expected. From the phase 1 results using amokinol suspension, once a day administration from an appropriate half life and stability in gastrointestinal tract were suggested.

2.3.P.2.3 Manufacturing Process Development

1) Risk Assessment of Manufacturing Process

A risk analysis was performed using Failure Mode and Effects Analysis (hereafter referred to as FMEA) to direct the establishment of the manufacturing process at the proposed commercial scale.

The details of FMEA is shown in Section 3.2.P.2.3. As for the definition of risk priority number (RPN), ≥40 was high risk, ≥20 to <40 was medium risk, and <20 was low risk.

As shown in Figure 2.3.P.2.3-1, drug substance partcle size, lubricant amount, blending time for lubricant and compression force may highly affect the drug product quality. Particle size of the API is a process input which affects critical quality properties, as shown in the initial risk assessment. Excipients and water control, which were identified as process inputs affecting important quality properties in the initial risk assessment, were deleted from the FMEA risk assessment items because employment of the direct compression decreased the control risk. On the other hand, the compression force was newly identified as a high risk and critical process parameter.

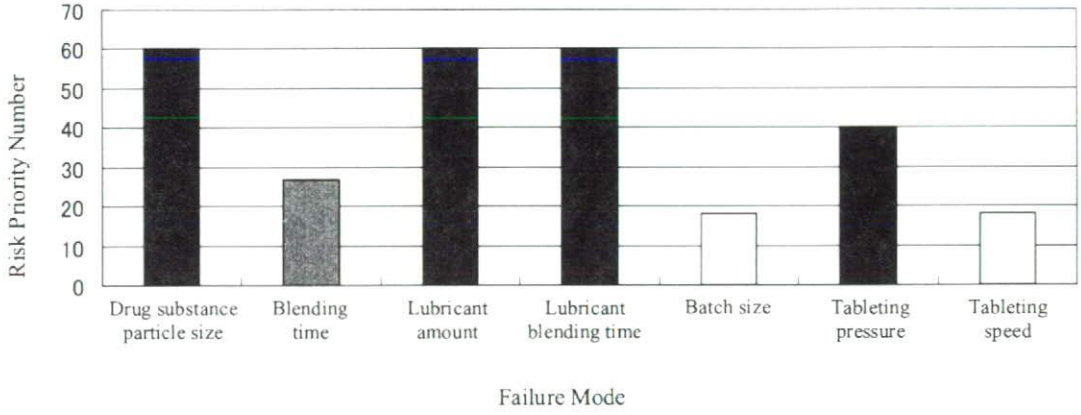


Figure 2.3.P.2.3-1 Results of FMEA Risk Analysis on Drug Product Composition and Manufacturing Process of Sakura Tablet

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, lubricantion 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 was measured using dissolution test method with a test fluid of 0.1% sodium lauryl sulphate. 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 is 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).

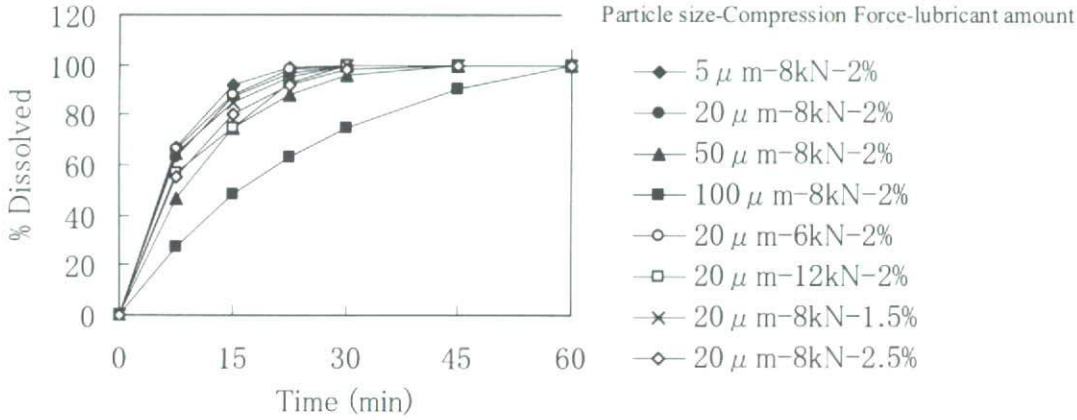


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Partcle Size (D90%), Compression Force and/or Lubricant Amount

2)-1-2 In vivo Evaluation

Following the confirmation in the above 2)-1-1, in vivo blood concentrations profiles of the API after administered tablets with composing different particle sizes. 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 partcle sizes of 100 □m, significantly lower Cmax and AUC were obtained, compared to ≤50□m particle size. In Section 2.5.2 Overview of Biopharmaceutics, details of this study were shown.

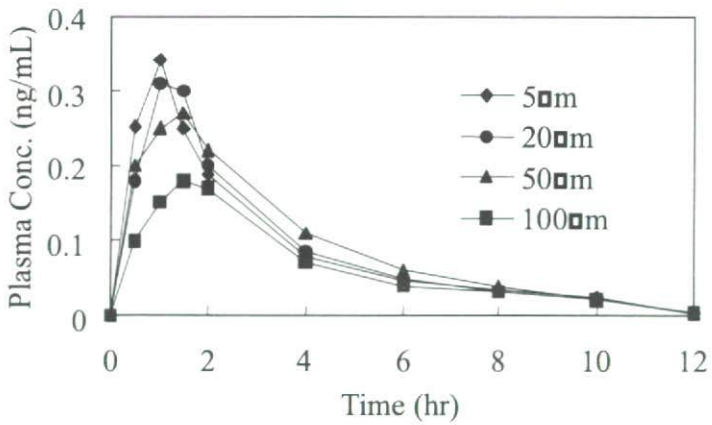


Figure 2.3.P.2.3-3 Blood Concentration Profiles

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 the results of 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. Design Space could be estrablished and the quality of manufactured tablets could be evaluated using this dissolution testing.

2)-2 Effect of drug substance partcle size

As shown in 2.3.P.2.3-2, dissolution rate became slow when a API with 100 μm particle size (D90) was composed, however when the size was within the range 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 ≤50□m particle size.

As described in 2.3.P.2.2 3) Initial Risk Assessment, due to the low solubility and 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. Taking into account the lower disslution rate, lower Cmax and extended Tmax according to increase of particle size of API, upper limit of particle size will be contlloed as 20□m.

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. From these results, it was confirmed about the affect on the dissolution or tablet hardness by these parameters, and the lubricant amount of 2% was justified.

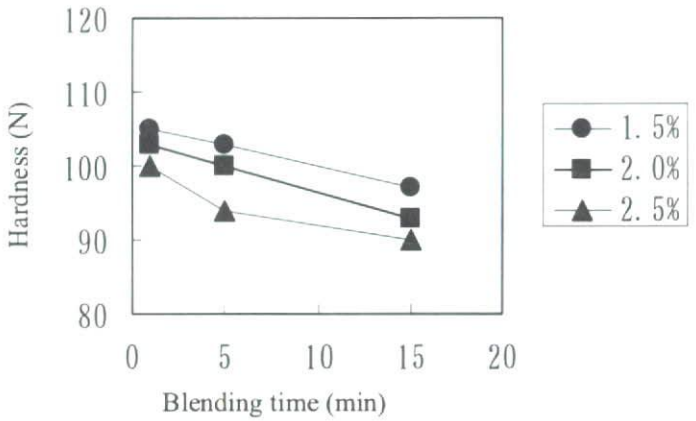


Figure 2.3.P.2.3-4 Correlation between Lubricant Amount, Lubrication Time and Tablet Hardness

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 dissoled 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 stirring feeder	Compression force kN	Content Uniformity	Dissolution (%) at 30 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 partcle 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 5 to 50 μm, and the target product profile were 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 was 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 partcle size (□m)	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 tableting method was employed. 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 were 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 partcle 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 was varied in the studied experimental range, the blending was stopped at the time when relative standard deviation (RSD) of blending homogeneity was <6%. However, the content uniformity must be affected by compression. Therefore, the belnding will be stopped at the time when RSD is less than 3%, taking into account the variation during the tableting process.

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

Variation factor:

- Time: 2 to 16 minutes
- Blending speed: 10 to 30 rpm
- Equipment: Drum type and V type blender
- Drug substance partcle 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 was evaluated, and the results were summarized in Figure 2.3.P.2.3-5. The figure shows that drug substance partcle 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 6 to 10 kN was confirmed.

	Clinical quality			Physical quality	
	Disolution	Assay	Content uniformity	Appearance	Hardness
Material characteristics					
Drug substance partcle size					
Lubricant SSA					
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 partcle 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. And, lubricant-blending process as low risk was also judged as critical process, because blending time should be controlled.

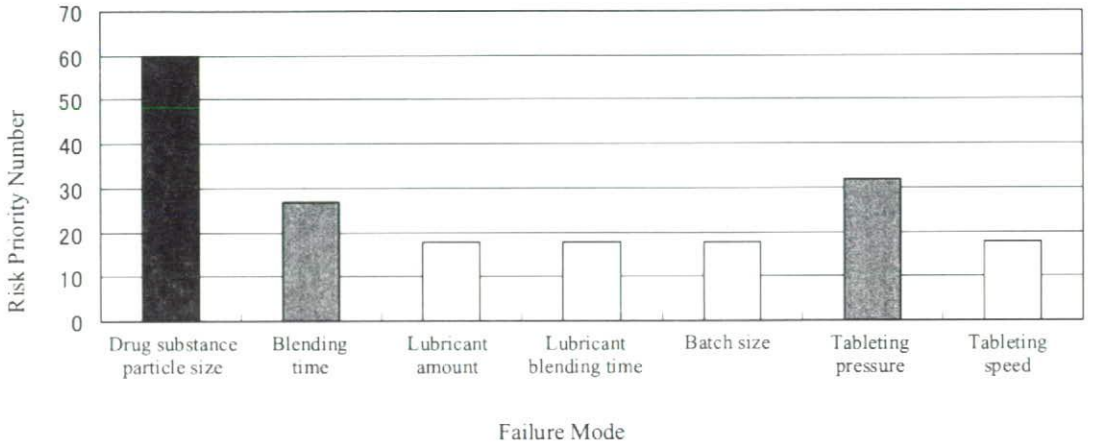


Figure 2.3.P.2.3-6 Results of FMEA Risk Assessment after Manufacturing Process Development for Sakura Tablet

6) Evaluation and Construction of Design Space

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 partcle size, lubricant SSA, lubricant blending time and mean 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 partcle size were largest for dissolution. Therefore, the Drug substance partcle 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 partcle 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, 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 <3%) 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.

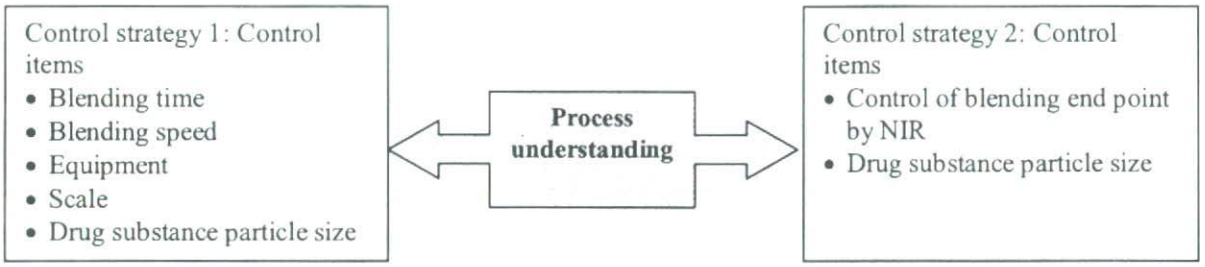


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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 partcle 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 partcle 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 onclinical 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 <3% 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 the commercial scale production process validation, although it was confirmed on a small scale that the lubricant amount of 2% was justified and blending time of 1 to 15 minutes did not affect the dissolution or hardness of the tablets remarkably.

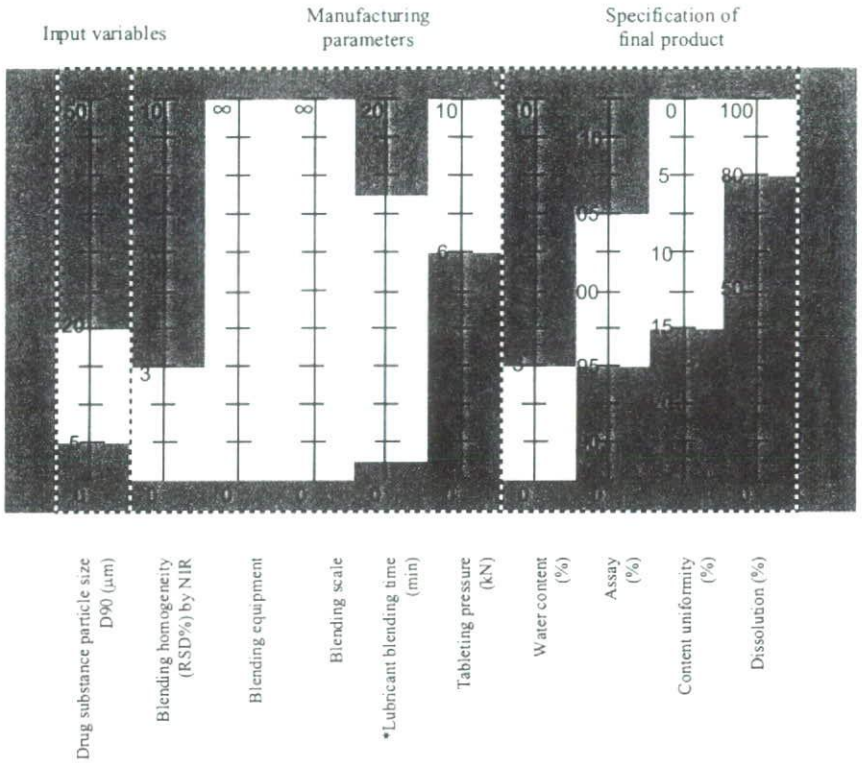
6)-2-2 Tableting Process

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 and Specifications of Sakura Tablet

7) Release Strategy of Final Drug Product

(1) Dissolution

For the drug substance partcle size, lubricant SSA, lubricant blending time and the mean tableting pressure which affected tablet quality as shown in Figure 2.3.P.2.3-5, 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.

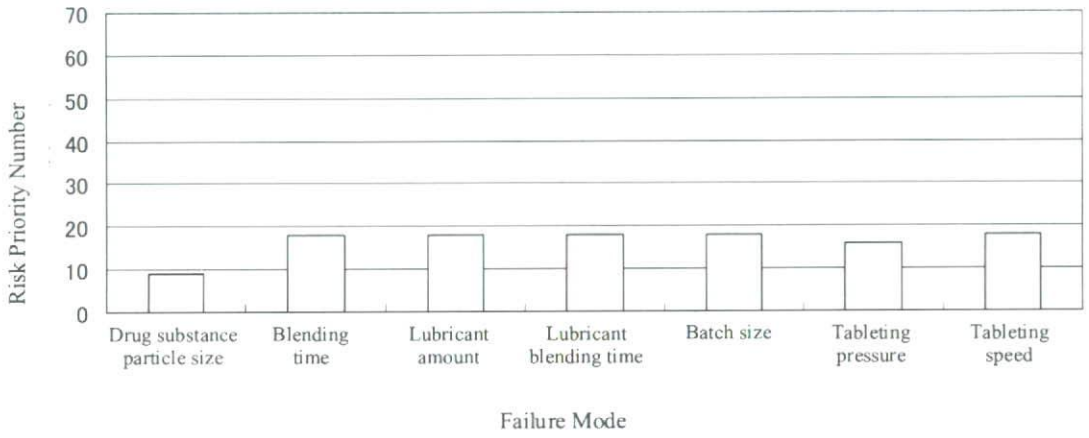


Figure 2.3.P.2.3-9 Results of FMEA Risk Analysis for Sakura Tablet after Control Strategy Implementation

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 (Sakura Tablet, Film-coated Tablet)

2.3.P.3.3 Manufacturing Process and Process Control

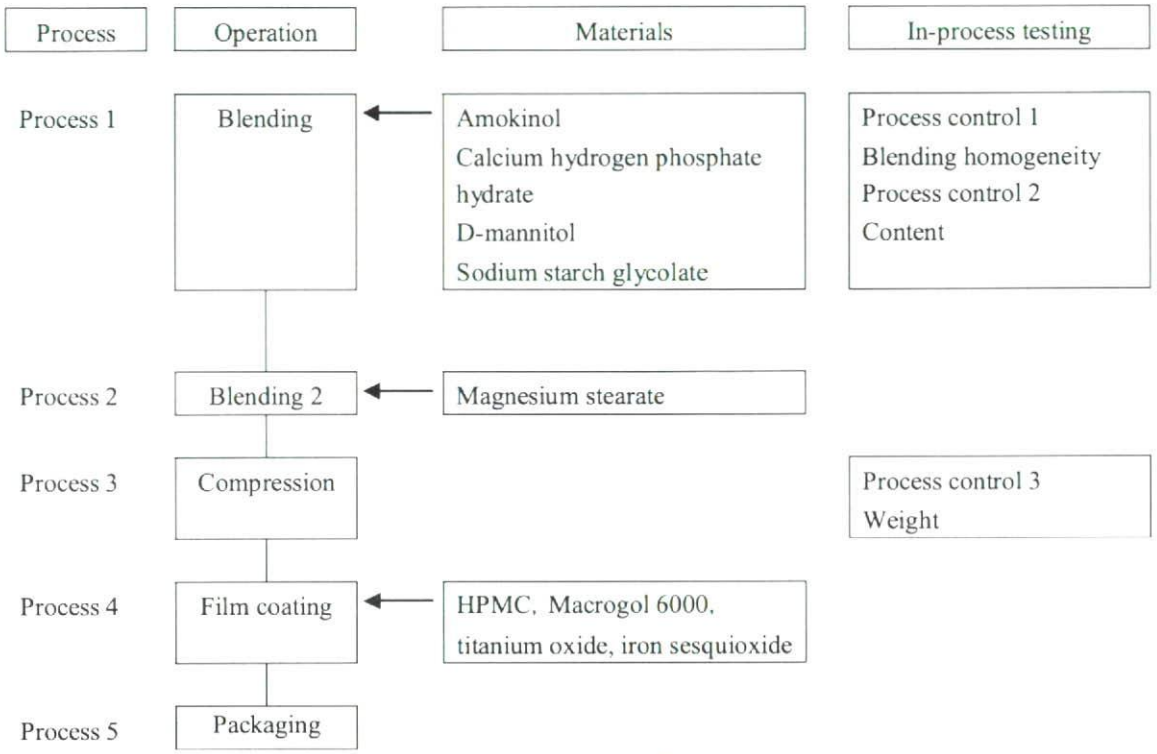


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

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.

We decided to perform real-time release, considering based on the results of drug product development in Section 2.3.P.2. that multiple forms of control can each serve as the specification test (dissolution test, content uniformity, and content (assay)) to maintain tablet quality as shown in Table 2.3.P.3.3.2.

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

As real-time release for dissolution test, we selected drug substance particle size and specific surface area of magnesium stearate used in manufacture, lubricant blending time and compression pressure at manufacturing as control variable, and decided to calculate the dissolution rate by multivariate formula using these 4 variables.

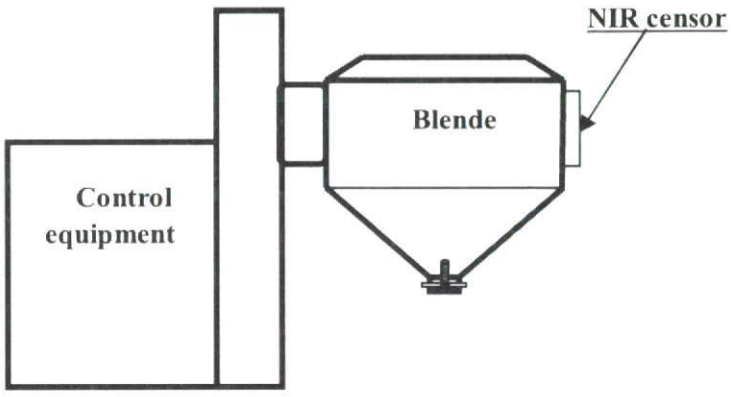
For the real-time release of content uniformity, monitoring of homogeneity by the in-line NIR at blending process and monitoring of the drug product weight calculated by tablet weight at compression process were employed.

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. Monitoring methods used in each process are described below.

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:

The content of blended powder employed in content RTR was determined using the test method described in [Content of blended powder: HPLC].



Determination conditions
Determination method: Diffuse reflection
Light source: High energy air cooled NIR source
Detector: A high-sensitive InGaAs detector
Scan range: 7,500 to 4,000 cm^{-1}
Number of scans: 16 scans.
Resolution: 8 cm^{-1}
Spectrum pre-treatment conditions: Multiplicative scatter correction (MSC)
Analytical method: Partial least squares (PLS).

[Blended homogeneity of the drug substance: RTR test method]
Determine the absorption spectrum from the outside of a blender operated at a blending speed of 10 to 30 rpm through borosilicate flat glass (thickness: about 1 mm) as directed under the Near-Infrared Spectrophotometry using diffusion reflection probe, and calculate the relative standard deviation from assayed values obtained at 6 consecutive time points.

Equation
Relative standard deviation (%) = X/s×100

$$s=\sqrt{\sum_{i=1}^{n}(xi-\overline{X})^2/(n-1)}$$

X: Mean of x_1, x_2, $\cdots x_n$
$x_1, x_2, \cdots x_n$: Content of active ingredient in individual tested samples