MHLW Sponsored Science Research Study

Establishing Design Space in critical steps and Control Strategy

Quality Overall Summary Mock P2 (Description Examples)

March 2009

This mock is prepared to show one approach based on the principles of ICH Q8, Q9 and Q10 guidelines. In order for readers to realize the principles into practices, thought processes of the development are described in detail. Because this mock is to present a scientifically sound case study of enhanced approach (design space and real time release) for discussion, the structure and style of the document or the technical content is NOT intended for recommendations as regulatory requirements.

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Table of Contents

2.3.P.1 Description and Composition of the Drug Product (Sakura Tablet, Film-coated Tablet)..... 2
2.3.P.2 Pharmaceutical Development (Sakura Tablet, Film-coated Tablet) 3
2.3.P.3 Manufacture (Sakura Tablet, Film-coated Tablet)..... 22
2.3.P.5 Control of Drug Product (Sakura Tablet, Film-coated Tablet) 33
3.2.P.2 Pharmaceutical Development (Sakura Tablet, Film-coated Tablet) 42

This mock-up is a scientific justified description example for applying the enhanced approach in Quality by Design, and is not mandatory requirements.

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MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

Generic name: Amokinol

2.3 QUALITY OVERALL SUMMARY

Sakura Tablet

2.3.P.1 Description and Composition of the Drug Product (Sakura Tablet, Film-coated Tablet)

The composition of Sakura Tablet is shown in Table 2.3.P.1-1.

Table 2.3.P.1-1 Composition of Sakura Table

Function	Specification	Excipient	Sakura Tablet 30 mg
Active ingredient	Separate specification	Amokinol	30 mg / tablet (103 mg)
Filler	JP	Calcium hydrogen phosphate hydrate	Appropriate amount
Filler	JP	D-mannitol	10 mg
Disintegrant	JP	Sodium starch glycolate	5 mg
Lubricant	JP	Magnesium stearate	2 mg
Coating agent	JP	HPMC	2.4 mg
Polishing agent	JP	Macrogol 6000	0.3 mg
Coloring agent	JP	Titanium oxide	0.3 mg
Coloring agent	JPES	Iron sesquioxide	Trace amount

2.3.P.2 Pharmaceutical Development (Sakura Tablet, Film-coated Tablet)

2.3.P.2.1 Composition of Drug Product

Physicochemical properties of amokinol, the active ingredient of Sakura Tablet, are shown in Section 2.3.S.1.3. General Properties. Amokinol is a neutral compound with a molecular weight of 450. And has moderately poor compression properties which could lead to difficulties in manufacturing robust tablets at high drug loading.

Solubility of amokinol in water is 0.015mg/mL at 20°C, making this compound practically insoluble in water. Solubility of amokinol in FaSSIF (Fasted State Simulated Intestinal Fluid) and HIF (Human Intestinal Fluidis 0.020 mg/mL. As shown in Figure 2.3.P.2.1-1, amount of amokinol dissolved in 250ml of buffer solutions is 4 mg over the pH range 1 to 8. As the amount of the active ingredient of Sakura Tablet is 30 mg, amokinol is classified as a low solubility compound according to Biopharmaceutical Classification (BCS). 1-octanol/water partition coefficient (logD) of amokinol is 2.6 at 25°C. Based on the result of permeability using Caco 2 cell membrane, amokinol is classified as a high permeability compound according to BCS.

From these results, amokinol is classified as a BCS class 2 compound (low solubility and high permeability).

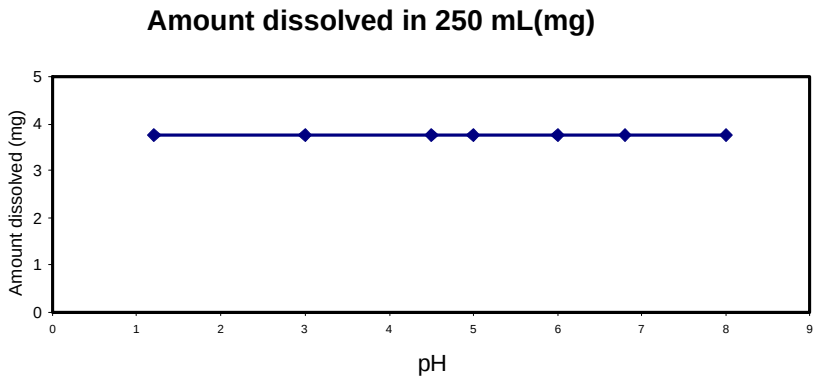


Figure 2.3.P.2.1-1 Solubility of Amokinol in Buffers of Various pH

Calcium hydrogen phosphate hydrate and D-mannitol were selected as diluents for Sakura Tablet, and sodium starch glycolate as a disintegrant, and magnesium stearate as a lubricant were also chosen.

Note)	The reason of choice of each excipient and results of their compounding test must be described in later sections.

2.3.P.2.2 Drug Product

1) Drug Product Development Strategy

For drug product development of Sakura Tablet, a more systematic approach (Quality by Design: QbD or Enhanced Approach) was employed, as well as conventional approaches based on experiences. In addition to prior knowledge and experiences of manufacturing, design of experiments and risk management for product quality were used. Moreover, continuous quality improvement during the entire product life cycle for formulation and manufacturing process of Sakura Tablet was intended by systematic evaluation, whcih is identification of critical quality attributes and critical steps of the API and the drug product, establishment of a design space, and a real time release based on deep understanding of the manufacturing process.

For construction of control strategy for the final manufacturing process and quality assurance of Sakura Tablet, the following approaches were employed.

1. Setting of Target Product Profile and early phase risk assessment
2. Risk assessment of composition and manufacturing process of the drug product
3. Identification of Critical Step and assessment of influence of the critical steps on Quality Attribute of the tablet
   - Study of the effects of particle size of the API on dissolution and in vivo absorption from the drug product
   - Study of level and lubrication process
   - Study of tableting process
   - Confirmation of main factors and interactions
4. Further evaluation of other variables on quality characteristics of the tablet
   - Study of effects on homogeneity of blending process
5. Assessment and construction of DS (Design Space)
6. Assessment and construction of RTR (Real Time Release) in critical processes
7. Review of the Risk assessment after implementation of the control strategy

According to the approach described above, Preliminary Hazard Analysis (PHA) was used in the initial risk assessment, and Failure Mode and Effects Analysis (FMEA) was used in the risk assessment of the manufacturing process and in the risk assessment after implementation of the control strategy. Risk assessment based on results of drug product development with Sakura Tablet manufactured in a pilot scale indicated that it was highly plausible that a particle size of the API affected the dissolution and that tableting pressure affected tablet hardness. Therefore, blending processes of granules for tableting and tableting process were selected as critical steps. However equivalent dissolution and in vivo absorption has been confirmed over the range 5 to 50 μm, although the particle sizes affected in vitro drug release from the tablet and in vivo pharamcokientics. Regarding tableting pressure, assessment results indicated low possibility that the pressure affects the quality of the final drug product; therefore it was judged that an appropriate quality could be kept by controling the tableting pressure in manufacturing. Finally, the design space of Sakura Tablet was constructed by input variables, process parameters and combination of final specifications of the final product (Figure 2.3.P.2.3-8 Design Space of Sakura Tablet).

Additionally, it was concluded that the real time releasing of products is possible on the following specificiation items: dissolution, content uniformity, and assay, by monitoring and cotrolling of both

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.

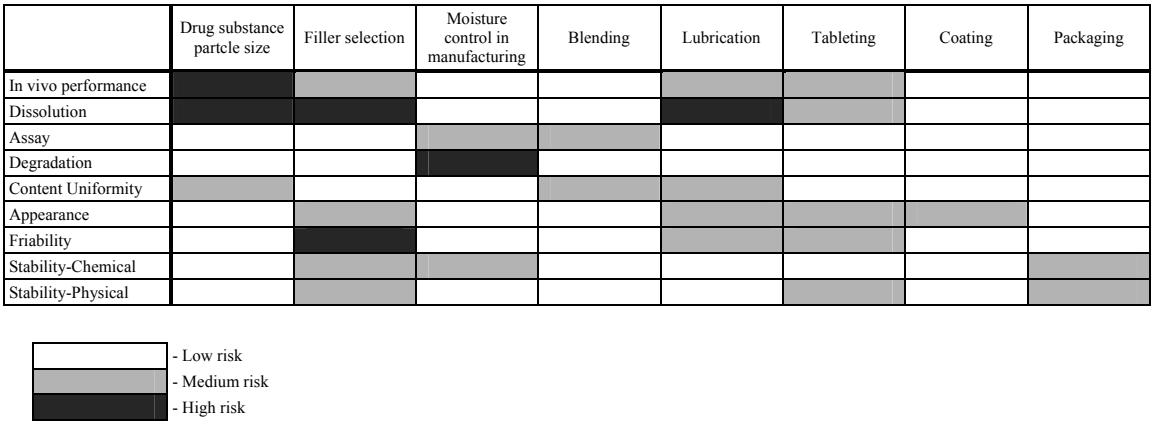


Figure 2.3.P.2.2-1 Summary of Initial Risk Assessment

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.

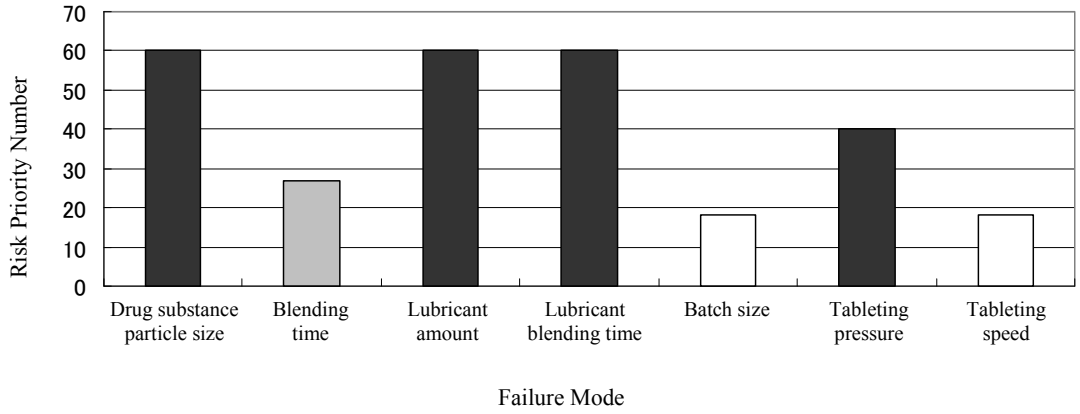


Figure 2.3.P.2.3-1 Results of FMEA Risk Analysis on Drug Product Composition and Manufacturing Process of Sakura Tablet

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).

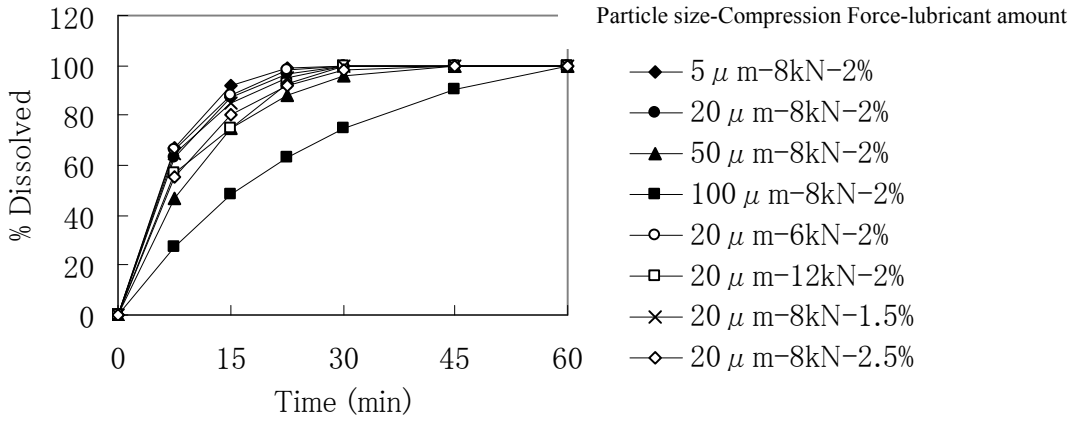


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Partcle Size (D90%), Compression Force and/or Lubricant Amount

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 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.

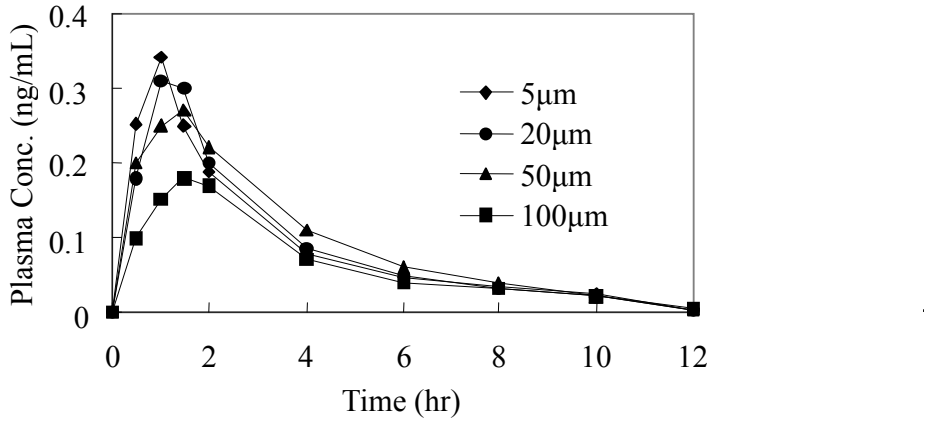


Figure 2.3.P.2.3-3 Blood Concentration Profiles

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 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 ≤50μm 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 20μm.

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.

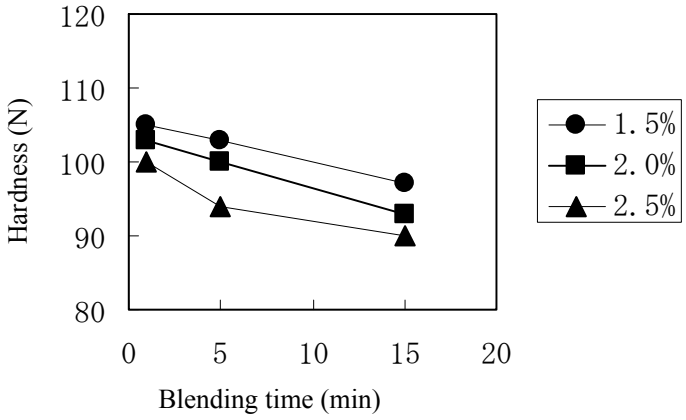


Figure 2.3.P.2.3-4 Correlation between Lubricant Amount, Lubrication Time and Tablet Hardness

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 (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 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.

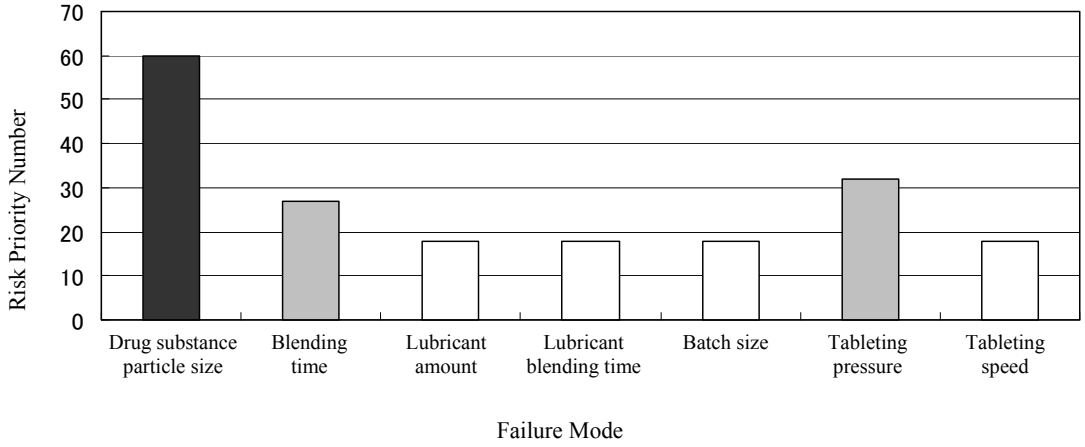


Figure 2.3.P.2.3-6 Results of FMEA Risk Assessment after Manufacturing Process Development for Sakura Tablet

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.

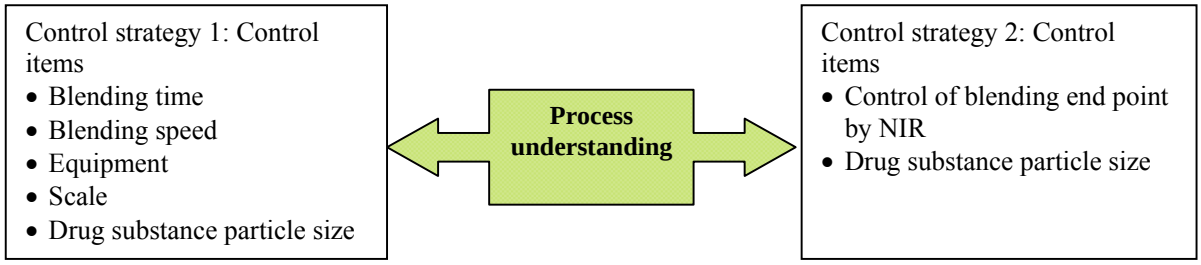


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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.

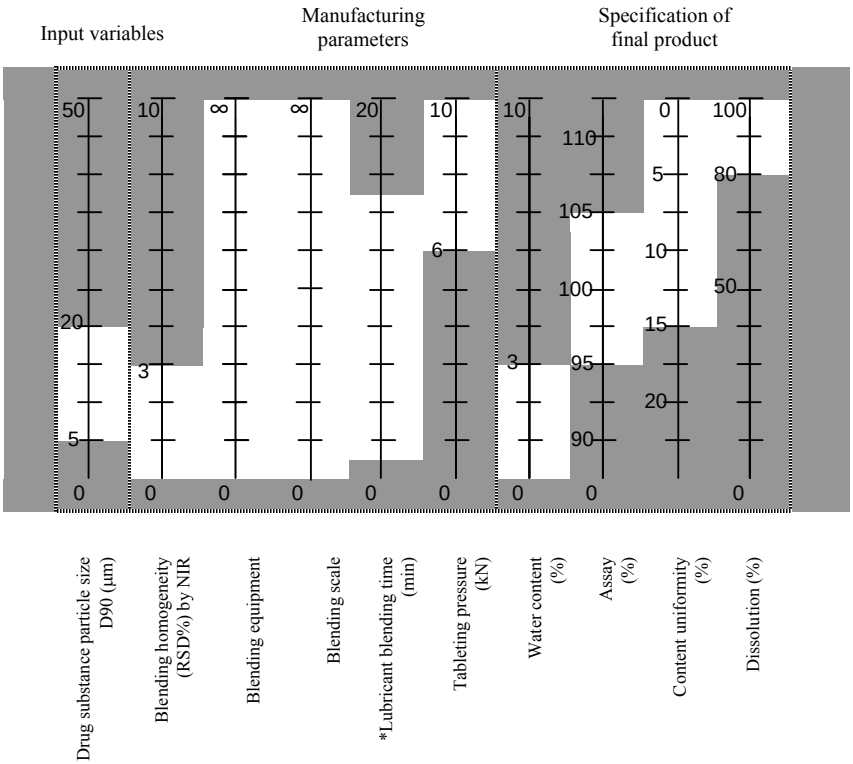
6)-2-2 Tableting Process

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.

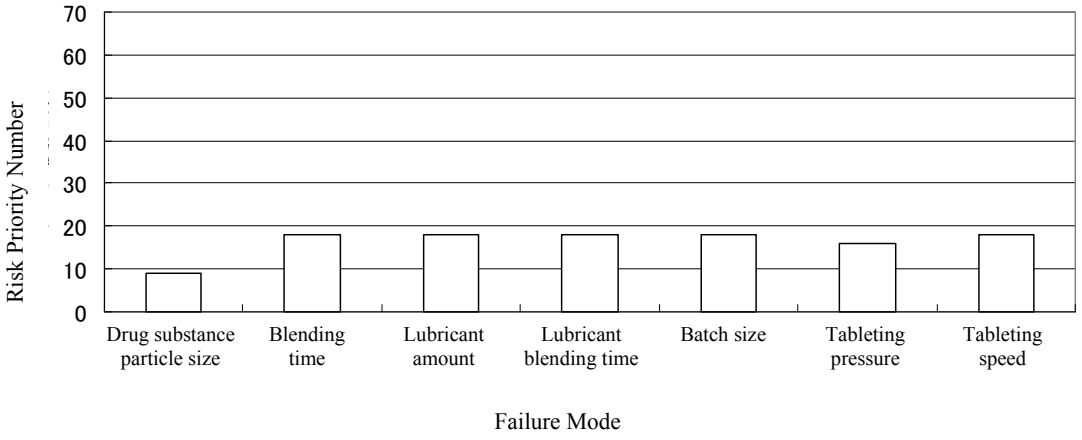


Figure 2.3.P.2.3-9 Results of FMEA Risk Analysis for Sakura Tablet after Control Strategy Implementation

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

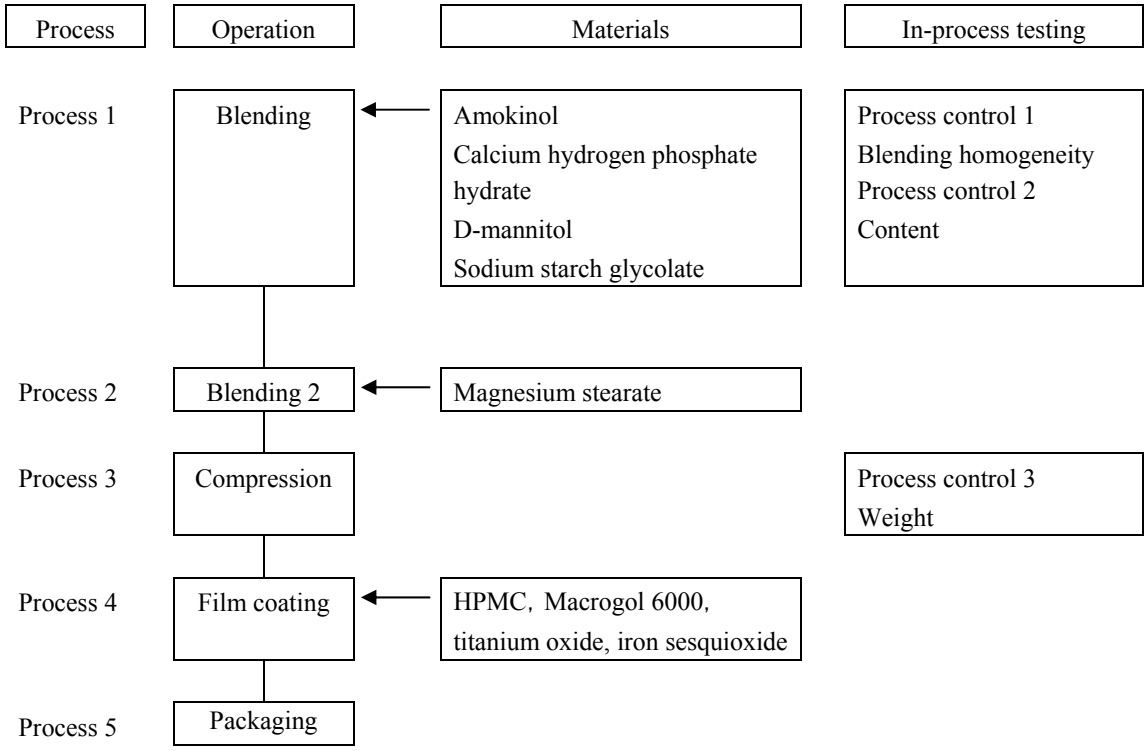


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

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.

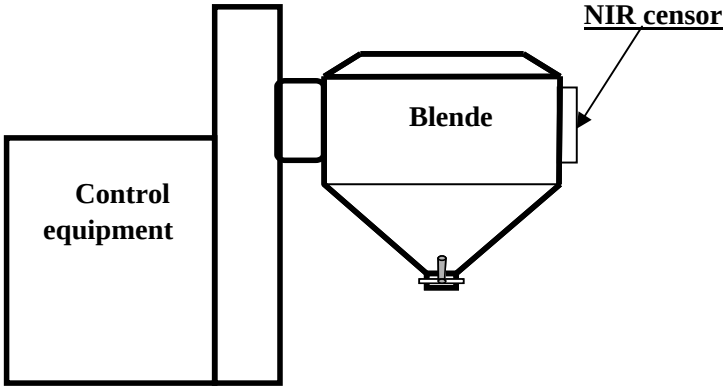
For the real-time release of content uniformity, monitoring of homogeneity by the in-line NIR at blending process and monitoring of the drug product weight calculated by tablet weight at compression process were employed.

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

n: Total number of tested samples
s: Standard deviation of samples

System suitability
System performance
Determine the content using the blended powder, demonstrated to contain about 100% of the active ingredient, by the controlled evaluation: it is 98.0% to 102.0% of the labeled amount.

Calibration and validation
Measurement at commercial production uses pre-treatment for spectrum measurement and analytical method used in constructing a calibration curve, and also uses the same measurement parameters as those in performing calibration. The validation is performed using measurement apparatuses to be used at commercial production in a scale reflecting actual production, and the calibration curve is validated using actually manufactured batches at appropriately determined intervals. The results are as described in '2.3.P.3.4.2 Validation of Test Methods (Analytical Procedures).'

Calibration
Blended powders with the additives at the same compounding ratio were prepared at 5 levels of the content of the active ingredient in a range from 70% to 130% of the labeled amount, and a calibration curve was constructed using MSC as pre-treatment for spectrum measurement and PLS as analytical method. As test of calibration model, the blended powder samples prepared containing the active ingredient in range from 70% to 130% of the labeled amount.

Validation
The obtained calibration curve was validated using 3 batches reflecting commercial production.

Periodic revalidation
It was decided that the calibration curve would validated using actually manufactured batches at appropriately determined intervals. The controlled validation to be used in calibration and validation used the blended powder content (HPLC) as shown below:

[Blended powder content: HPLC]
Weigh accurately XX mg of the blended material, add exactly XX mL of the internal standard solution, and shake well for XX minutes. Centrifuge this solution, to XX mL of the supernatant add XX mL of the mobile phase, and use this solution as the sample solution. Separately, weigh accurately X.XXX g of Amokinol Reference Standard, dissolve in the mobile phase to make exactly XX mL. Pipet XX mL of the solution, add the mobile phase to make XX mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution according to the following conditions. Determine each peak area, Q_T and Q_S, of the solutions by the automatic integration method.

Amount (mg) of amokinol ($C_{XX}H_{XX}N_XO_X$) = $W_S \times Q_T/Q_S \times$ X.XXX
W_S: Amount (mg) of Amokinol Reference Standard

Internal standard solution: A solution of benzophenone in a mixture of acetonitrile and water (1:1) (1 in 2000)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of acetonitrile and water (1:1).

Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability

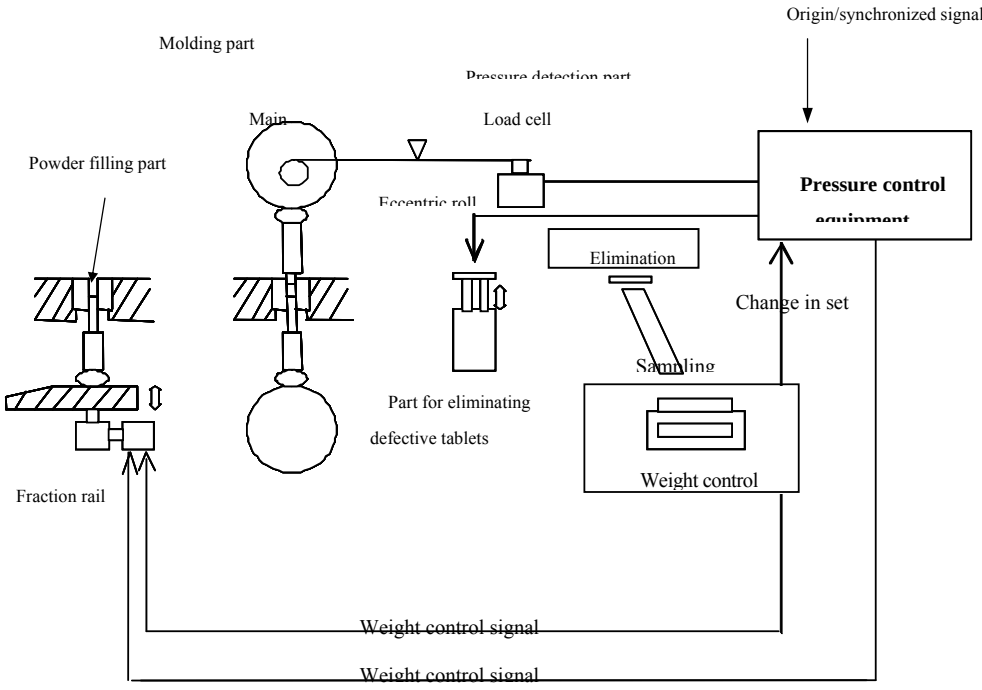
System performance: Proceed with 20 μL of the standard solution under the above operating conditions. Amokinol and the internal standard are eluted in this order, and a resolution between their peaks is not less than XX.

System reproducibility: Repeat the test six times with 20 μL of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

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. A compression pressure controller allows correction of the amounts of filled blended powder (filling depth) and removal of tablets out of the acceptable range from the system based on the information on measured compression pressure. In addition, the mean weight information periodically measured by automatic sampling is fed back to the compression pressure control equipment, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression pressure control equipment was also selected.

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 six 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.

Taking into consideration the case where blending homogeneity evaluation other than monitoring by NIR is needed, the content of blended powder (HPLC) has been set in 2.3.P.3.3.3. The test will be performed on blended powder from 6 sampling points. The same control range as the acceptable range by NIR has been employed.

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: less than 3.0%

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	Less than 2%

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 (cm^2/g) - 0.1849 × lubricant blending time (min) - 3.783×10^{-2} × compression pressure (N)

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 cm^2/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 was determined over the manufacturing process. The process control ranges from these tests 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

The blended powders containing the active ingredient at 5 levels ranging from 70 to 130% of the labeled amount were used. Samples were taken from 10 sampling points at each level of blended powder. This procedure was repeated 3 times on different blended powders, and a total of 150 samples were used for construction of a calibration curve. The determination of observed values used the assay (HPLC) in drug product homogeneity in the specifications and test methods as the controlled evaluation for validation. The results of the constructed calibration curve confirmed a good linearity and correlation with observed values in a range of ±30% of theoretical content value.

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 used for the validation. As in calibration, the validation was performed on blended powder samples prepared at 5 levels ranging from 70 to 130% of the active ingredient, and the results were, as shown in Table 2.3.P.3.4.2-2, favorable.

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

[3] Test of commercial production facilities

A total of 30 values measured on 10 samples each of 3 batches of blended powdered manufactured in a commercial manufacturing scale were incorporated into the calibration curve constructed in [1], and the curve was corrected. NIR measured values obtained from the batches manufactured in a commercial manufacturing scale and the results of HPLC showed a good correlation.

2.3.P.3.5 Process Validation and/or Evaluation

For the items employed in the real-time release tests, calibration will be performed again if the production scale is changed. In the registration step, three batches manufactured in the pilot scale were evaluated. The first three commercial batches will be evaluated .

2.3.P.3.5.1 Blending Process (Evaluation Results Concerning Content Uniformity)

All results of homogeneity measured in the blending process with three batches manufactured in the pilot scale indicated completion of the blending process within the control range.

Content uniformity after compression was confirmed using Ultraviolet-visible Spectrophotometry. The uniformity values were 96.4% to 102.3% of the labeled amount and its RSD values were 1.4% to 1.8%. Therefore all batches met the criteria of Content Uniformity in General Tests, Processes and Apparatus.

Table 2.3.P.3.5.1-1 Comparison of Content Uniformity Results

	Content (%)		
	Batch XX1	Batch XX2	Batch XX3
Mean	99.8	100.1	101.4
RSD	1.2	1.5	1.4
Result by ultraviolet-visible spectrophotometry			
Mean (min-max)	97.9 (96.4-102.1)	99.1 (97.4-101.0)	100.3 (96.5-102.3)
Relative standard deviation (%)	1.6	1.4	1.8
Determined value	4.4	3.3	4.4

2.3.P.3.5.2 Blending Process (Results of Dissolution Test Evaluation)

For three batches manufactured in the pilot scale, all results of the drug substance particle size, specific surface area of magnesium stearate, lubricant blending time and dissolution rate calculated from the compression pressure were within the control ranges. With three batches of Sakura tablets, it was confirmed that the dissolution of each batch in 30 minutes were 88.4% to 102.5% and met the criteria of the dissolution test.

Table 2.3.P.3.5.2-1 Comparison of Dissolution

	Batch Data		
	Batch XX1	Batch XX2	Batch XX3
Drug substance particle size	X	X	X
Specific surface area of magnesium stearate	XX	XX	XX
Lubricant blending time	XX	XX	XX
Compression pressure	XXX	XXX	XXX
Result of multivariate analysis	89.8	87.3	88.5
Dissolution test results Mean (min-max)	92.8 (88.4 - 94.2)	90.3 (89.0 - 102.5)	91.5 (90.5 - 93.5)

2.3.P.3.5.3 Compression Process (Results of Content Evaluation)

For three batches manufactured in the pilot scale, all results of blended powder content and contents calculated from tablet weight after the compression were within the control ranges. It was confirmed that the content determined using the content test (HPLC method) after compression was 98.4% to 100.2%, which met the criteria in the specifications.

Table 2.3.P.3.5.3-1 Results of Tablet Weight and Content

	Weight (mg)		
	Batch XX1	Batch XX2	Batch XX3
Mean	99.5	100.3	99.1
Relative standard deviation (%)	0.9	1.2	1.5
Results of content by HPLC	98.4%	100.2%	99.1%

2.3.P.5 Control of Drug Product (Sakura Tablet, Film-coated Tablet)

The specifications and test methods for Sakura Tablet were set based on the results of Drug Product Development, Stability results and the analytical results of the batches that were manufactured in the pilot scale.

2.3.P.5.1 Specifications and Test Methods

Real-time release is employed for the release test items of Sakura Tablet, content uniformity, dissolution test and content (assay). The summary of the method for real-time release control applied to the items in the Specifications and the test methods have been described. The summaries and criteria for the critical specifications and test methods in the control strategy have also been described.

Table 2.3.P.5.1-1 Specifications and Test Methods

Test items		Test methods	Specification
Appearance		Visual inspection	White plain tablet
Identification	Ultraviolet-visible spectrum	Ultraviolet-visible spectrophotometry (acetonitrile/water mixture (1:1))	Amokinol exhibits similar intensities of absorption at the same wavelength, compared to the reference standard.
Purity	Related substances	HPLC method (absolute calibration curve method)	Individual related substance: Not more than 0.2% Total related substances: Not more than 1.0%
Content uniformity		Omitted. Because Content Uniformity of amokinol in the blending process and compression pressure in the compression process are monitored.	
Content uniformity (*)		Ultraviolet-visible spectrophotometry (acetonitrile/water mixture (1:1))	Meet the criterion of drug product homogeneity (Content Uniformity)
Dissolution test		Omitted. Because drug substance particle size, specific surface area of magnesium stearate, lubricant blending time and compression pressure are monitored for control.	
Dissolution test (*)		Apparatus: Paddle method Test fluid: 0.1% sodium lauryl sulfate Test fluid volume: 900 mL Rotating speed: 50 rpm Assay: HPLC method (absolute calibration curve method)	Dissolution rate in 30 minutes 80% (Q)
Content (assay)		Based on the content of the blended powder in the blending process and on the weight in the compression process.	
Content (assay*)		HPLC method (internal standard)	95.0% to 105.0% of labeled amount

* To be used for items described in Section 2.3.P.2.3 Manufacturing Process Development (10) Control Strategy.

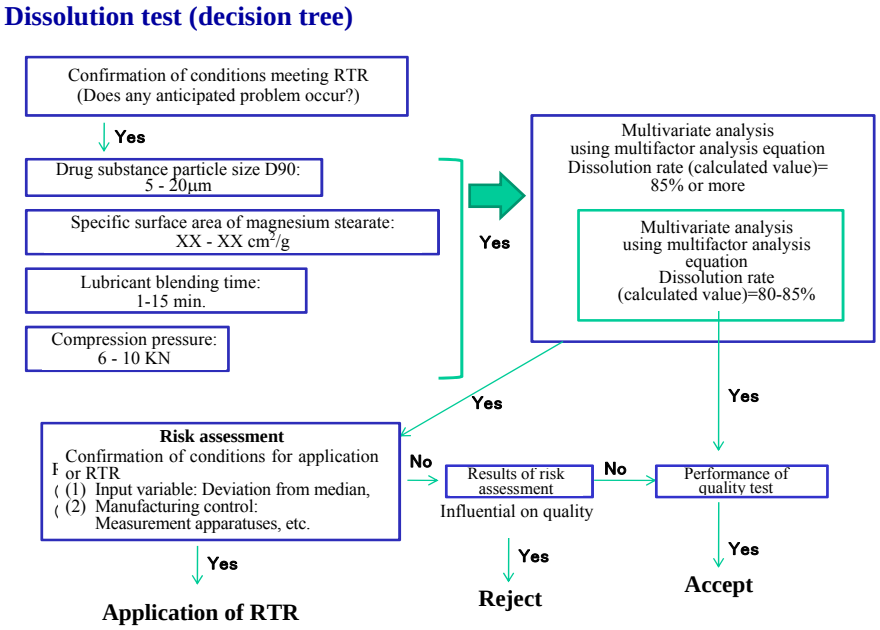
2.3.P.5.2 Test Methods (Analytical Procedures)

Note) Only dissolution test, content uniformity and assay are described because real release testings are set for those items. Other analytical procedures must be described.

Real time release was employed for content uniformity, the dissolution test and content (assay). For validation of the test methods and analytical procedures, those used in the real-time release are described in Section 2.3.P.3.4 Management of Critical Processes and Critical Intermediates. The real-time release procedures are described for each item of real-time release tests. The quality test methods performed according to the control strategies such as the results of risk assessment and change in manufacturing site and in stability testing are described.

2.3.P.5.2.1 Dissolution Test

The real-time release procedures are performed according to the following flow chart.



(1) After 3rd process of amokinol drug substance (pulverization of amokinol), drug substance particle size, specific surface area of magnesium stearate in the control of raw materials for Sakura tablets, blending time at 2nd blending process, and compression pressure at 3rd process (compression process) are confirmed to meet the in-process control values.

(2) The dissolution rate is calculated from the following equation, and the rate which is 85% or more is considered acceptable.

Dissolution rate (%) to the labeled amount of amokinol (CxxHxxNxOx) = 108.9 – 11.96 × drug substance particle size $[\log_{10}(d(0.9))]$ – 7.556 × 10^{-5} x specific surface area of magnesium stearate (cm^2/g) – 0.1849 × lubricant blending time (minutes) – 3.783*10^{-2} × compression pressure (N)

When the dissolution rate is 80-85%, the dissolution rate is calculated from the second dissolution test, and the rate which is 80% (Q) or more is considered acceptable.

Take 1 tablet of Sakura Tablets, and perform the test at 50 rpm as directed in the Paddle Method, using 900 mL of 0.1% sodium lauryl sulfate TS. Take not less than 20 mL of the dissolved solution at 30 minutes after starting the test, and filter through a membrane filter (not more than 0.45 μm in pore size). Discard the first X mL of the filtrate, pipet subsequent *V* mL, add 0.1% sodium lauryl sulfate TS to make exactly *V'* mL of a solution containing about XX μg of amokinol (CxxHxxNxxOx) per mL according to the labeled amount, and use this solution as the sample solution.

Separately, weigh accurately about X.XX g of amokinol reference standard, add XX mL of 0.1% sodium lauryl sulphate TS to make exactly XX mL. Pipet 1 mL of this solution, add 0.1% sodium lauryl sulfate TS to make exactly XX mL, and use this solution as the standard solution. Perform the test with the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine peak areas, A_T and A_S, of amokinol in each solution by the automatic integration method.

Dissolution rate (%) to the labeled amount of amokinol (CxxHxxNxOx) = $W_S \times A_T/A_S \times V'/V \times 1/C \times X.XXX$

W_S: Amount (mg) of amokinol reference standard

C: Labeled amount (mg) of amokinol (CxxHxxNxOx) per tablet

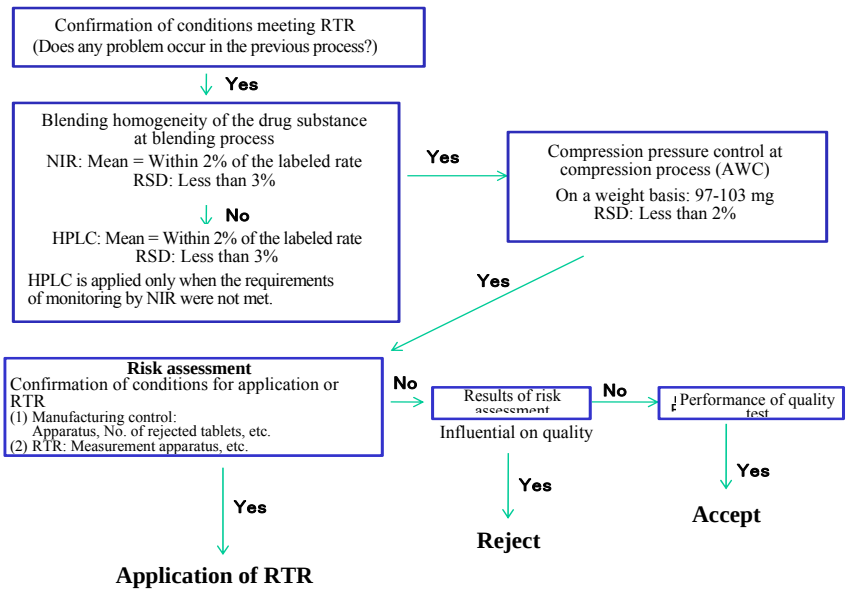
Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column about 4.6 mm in inside diameter and 15cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase: A mixture of acetonitrile and water (1:1).
Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability
System performance: Proceed with 20 μL of the standard solution under the above operating conditions. Amokinol and the internal standard solution are eluted in this order, and a resolution between their peaks is not less than XX.
System reproducibility: Repeat the test six times with 20 μL of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

2.3.P.5.2.2 Content Uniformity

The real-time release procedures are performed according to the following flow chart.

Content uniformity test (decision tree)



The blending homogeneity at the 1st process (blending process) and tablet weight at the 3rd process (compression process) are confirmed to meet the in-process control values.
When the results obtained by NIR cannot be employed in blending homogeneity monitoring at blending process, and the test is performed on samples taken from 6 sampling points according to the content of blended powder (HPLC) described in 2.3.P.3.3.1.

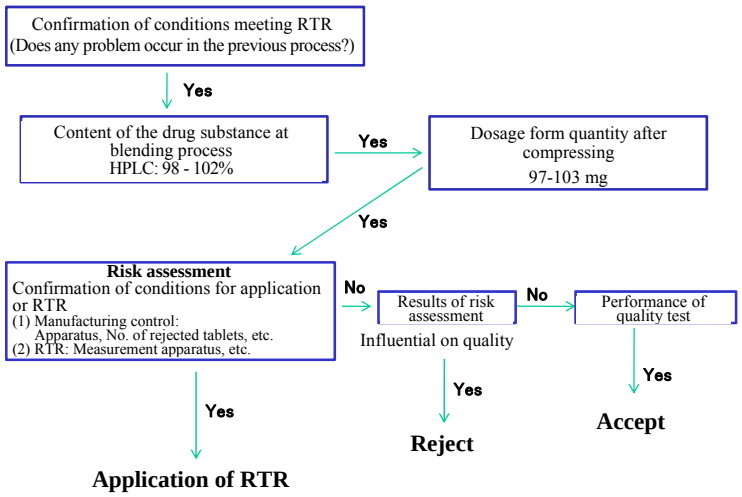
When it is judged from the results of risk assessment that quality test is necessary, the content uniformity test is performed by the following method: the requirements are met.
Take 1 tablet of Sakura tablets, add 50 mL of a mixture of acetonitrile and water (1:1), shake until the tablet is disintegrated, radiate ultrasound for 10 minutes, and add a mixture of acetonitrile and water (1:1) to male exactly 100 mL. Filtrate this solution through a membrane filter (0.45 μm in pore size), and use the filtrate as the sample solution. Separately, weigh accurately about X.XX g of amokinol reference standard, dissolve in a mixture of acetonitrile and water (1:1) to make exactly *V* mL. Pipet 5 mL of this solution, add a mixture of acetonitrile and water (1:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Ultraviolet Visible Spectrophotometry and determine absorbance of A_T and A_S at 284 nm using a mixture of acetonitrile and water (1:1) as the blank.

Amount (mg) of amokinol = $W_S \times A_T/A_S \times$ X.XXX
W_S: Amount (mg) of amokinol reference standard

2.3.P.5.2.3 Content (assay)

The real-time release procedures are performed according to the following flow chart.

Content (decision tree)



The amount of amokinol is calculated by the following equation.

Amount (%) to labeled amount of amokinol (CxxHxxNxxOx) = Content (%) of amokinol in blended powder at 1st process (blending process) × tablet weight (mg) after 3rd process (compression)/*C*
C: Labeled amount (mg) of amokinol (CxxHxxNxOx) per tablet

When it is judged from the results of risk assessment that the quality test is necessary, the amount of amokinol is measured by the following assay method.

Weigh accurately, and powder not less than 20 Sakura tablets. Weigh accurately a portion of powder, equivalent to about X.XXX g of amokinol according to the labeled amount, add exactly XX mL of the internal standard solution, and shake thoroughly for XX minutes. Centrifuge this solution, to XX mL of the supernatant add the mobile phase to make XX mL, and use this solution as the sample solution.

Separately, weigh accurately about X.XXX g of amokinol reference standard, dissolve in the mobile phase to make exactly XX mL. Pipet XX mL of this solution, add the mobile phase to make XX mL, and use this solution as the standard solution. Perform the test with 20 µL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine peal areas, QT and QS, of amokinol in each solution.

Amount (mg) of amokinol (CxxHxxNxOx) = $W_S \times Q_T/Q_S \times$ X.XXX
W_S: Amount (mg) of amokinol reference standard
Internal standard solution = A solution in a mixture of acetonitrile and water (1:1) (1 in 2000)

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column about 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about 40°C.
Mobile phase: A mixture of acetonitrile and water (1:1).
Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability
System performance: Proceed with 20 μL of the standard solution under the above operating conditions. Amokinol and the internal standard are eluted in this order, and a resolution between their peaks is not less than XX.
System reproducibility: Repeat the test six times with 20 μL of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

2.3.P.5.3 Validation of Test Methods (Analytical Procedures)

Note: Only dissolution test is decribed

2.3.P.5.3.1 Dissolution Test

Analytical validation is as summarized in Table 2.3.P.5.3-1, and has been shown by the results of linearity, accuracy, and precision to be suitable as analytical method.

Table 2.3.P.5.3.1-1 Summary of Validation of Analytical Procedure

Items		Results
Linearity	Correlation coefficient	r = 0.99994
	Regression formula	y = 0.00191x + 0.00090
	Residual sum of squares	6.8694×10^{-6}
Range (%)		0 to 150
Accuracy	Recovery rate (%)	100.6
	95% confidence interval of accuracy	-1.94 to 2.94
Repeatability	Standard deviation	0.84
	Relative standard deviation (%)	0.84
	95% confidence interval of standard deviation	0.60 to 1.44
Intermediate precision	Standard deviation	0.8
	Relative standard deviation (%)	0.8
	95% confidence interval of standard deviation	0.7 to 1.0

2.3.P.5.3.2 Content Uniformity

2.3.P.5.3.3 Content (Assay)

2.3.P.5.4 Batch Analyses

2.3.P.5.5 Characterisation of Impurities

2.3.P.5.6 Justification of Specification and Test Methods

Note: Only dissolution test is decribed

2.3.P.5.6.1 Dissolution Test

It has been decided to control drug substance particle size, specific surface area of magnesium stearate, blending time at 2nd blending process, compression pressure as real-time release in place of the dissolution test. When the dissolution rate (%) calculated from these 4 items is not less than 85%, the real-time release was considered acceptable taking into account the separately established quality test specification, dissolution rate (%) = 80%Q. When the calculated dissolution rate is 80-85% and the results of risk assessment indicates that this is not considered to affect the quality, the separately established quality tests is performed on the batch in issue.

2.3.P.5.6.1.1 Justification of Specification and Methods of Dissolution Test

Setting of dissolution test using the paddle method, in accordance with JP general tests, processes and apparatus was investigated. The dissolution rate was assayed by HPLC method.

With tablets manufactured in processes with varied parameters (refer to P.2.3. Manufacturing Process Development), dissolution tests were performed using each of the test fluids, Solution 1 and Solution 2, under the following conditions: solvent volume = 900 mL, 50 rpm. Not all the tablets were fully dissolved under these conditions.

Then, 0.1% polysorbate 80 was added to the test fluids. Although the compounded tablets were nearly 100% dissolved after 15 minutes, it was not possible to discriminate each tablet batch as shown in Figure 2.3.P.5.4-1.

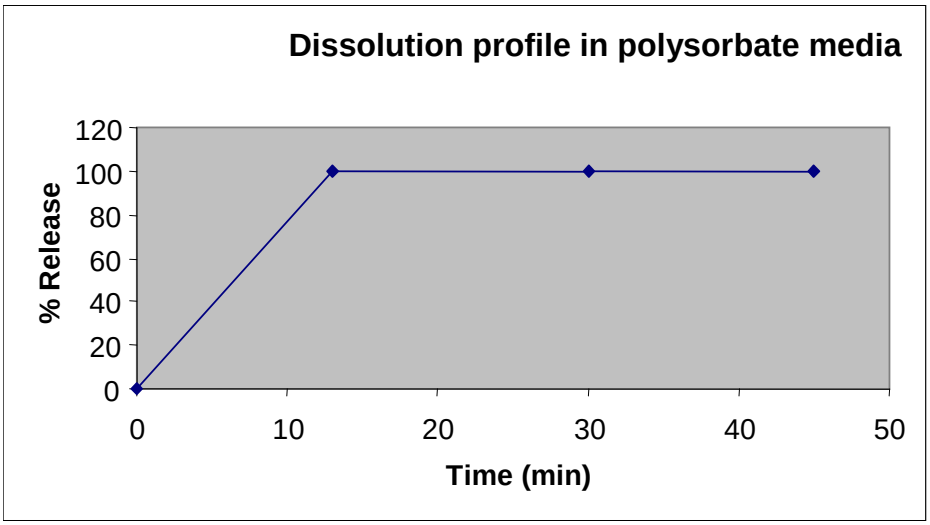


Figure 2.3.P.5.4-1 Dissolution Profiles in the Polysorbate 80 Added Test Fluids

In addition, the dissolution test method was evaluated in a test fluid with 0.1% sodium lauryl sulphate. The results indicated that sufficient discrimination capability and dissolution were obtained using this test fluid as shown in Figure 2.3.P.5.4-2.

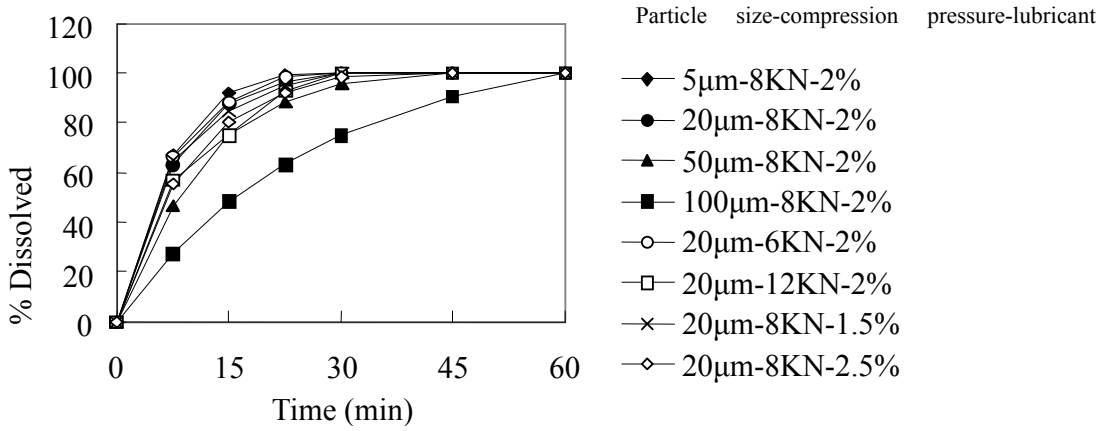


Figure 2.3.P.5.4-2 Dissolution Profiles in 0.1% Sodium Lauryl Sulphate Test Fluid

Based on the above results, the test fluid of 0.1% sodium lauryl sulphate was chosen in which a difference in the dissolution of the inter-products was observed. A sampling point at 30 minutes after start of dissolution was selected, where the dissolution profiles become steady.

As the linearity, accuracy and precision were all satisfactory, as shown in Table 2.3.P.5.3-1 Summary of Validation of Analytical Procedure, the analytical procedures have been justified.

2.3.P.5.6.2 Content Uniformity

2.3.P.5.6.3 Content (Assay)

MODULE 3: Quality

Generic name: Amokinol

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

Sakura Tablet

3.2.P.2 Pharmaceutical Development (Sakura Tablet, Film-coated Tablet)

3.2.P.2.2 Drug Product

3) Initial Risk Assessment

Preliminary Hazard Analysis (PHA)[1] was used for the initial risk assessment.

First, the following quality attributes were listed as below from the target product profile of Sakura Tablet.

- *In vivo* performance
- Dissolution
- Assay
- Degradation
- Content uniformity
- Appearance
- Friability
- Chemical stability
- Physical stability

Material attributes and processes that are likely to affect tablet quality attributes were selected as hazards from process inputs, and listed as below.

- Drug substance particle size
- Filler selection
- Moisture control in manufacturing process
- Blending
- Lubrication
- Compression
- Coating
- Packaging

The severity and probability of risks on which each hazard has an effect are rated during risk assessment using PHA.

Definitions of severity and probability are shown in Figure 3.2.P.2.2-1.

Severity	Score
Minor	1
Major	2
Critical	3
Catastrophic	4

Probability	Score
Very unlikely	1
Remote	2
Occasional	3
Probable	4
Frequent	5

Figure 3.2.P.2.2-1 Definition of Severity and Probability in PHA

The risk assessment in this development stage were qualitatively evaluated by team members who are responsible for developing the drug product, based on experience in the development of drug products, namely oral solid dosage and research data of Sakura Tablet. The results of the evaluation were discussed and confirmed by the team members. When the rating given by the team members differed, the higher risk rating was employed.

[1)] *Preliminary Hazard Analysis*, Marvin Rausand, Norwegian University of Science and Technology, May 2005

Criteria for severity and probability are qualitatively shown in Figure 3.2.P.2.2-2. The degree of each definition is shown below.

Severity

- Catastrophic: Products will be recalled by the degree of effects of the hazard.
- Critical: The manufacturing line will be stopped (product shortage will occurred) by the degree of effects of the hazard.
- Major: Products will be deviated by the degree of effects of the hazard.
- Minor: No effects on the product quality properties.

Probability

- Frequent: Outbreak frequency not less than about once per month, assuming the manufacture of about 100 lots per year
- Probable: Outbreak frequency about once per month
- Occasional: Outbreak frequency about once per year
- Remote: Outbreak frequency about once every 10 years
- Very unlikely: Outbreak frequency about once every 100 years or less

Each hazard was rated by their severity and probability, then classified into high risk (H), medium risk (M) or low risk (L) according to the risk rating table shown in Table 3.2.P.2.2-2.

Hazards with high risk or medium risk must be controlled as low risk by the control strategy from the drug product design.

Probability / Severity	1	2	3	4	5
Catastrophic: 4	M	H	H	H	H
Critical: 3	L	M	M	H	H
Major: 2	L	L	M	M	H
Minor: 1	L	L	L	M	M

H High risk
M Medium risk
L Low risk

Table 3.2.P.2.2-2 Risk Ranking of Preliminary Hazard Analysis

The results of the actual score rating and risk ranking using the PHA described above are shown in Table 3.2.P.2.2-1 and summarized in Figure 3.2.P.2.2-3.

Table 3.2.P.2.2-1 Results of PHA

Hazard	Event	Severity	Probability	Risk score
Drug substance particle size	*In vivo* performance	3	5	H
Drug substance particle size	Dissolution	3	5	H
Drug substance particle size	Assay	3	1	L
Drug substance particle size	Degradation	2	1	L
Drug substance particle size	Content uniformity	3	3	M
Drug substance particle size	Appearance	1	1	L
Drug substance particle size	Friability	1	2	L
Drug substance particle size	Stability – chemical	1	2	L
Drug substance particle size	Stability – physical	1	2	L
Filler selection	*In vivo* performance	3	3	M
Filler selection	Dissolution	3	4	H
Filler selection	Assay	1	2	L
Filler selection	Degradation	1	3	L
Filler selection	Content uniformity	2	2	L
Filler selection	Appearance	3	3	M
Filler selection	Friability	4	4	H
Filler selection	Stability – chemical	3	3	M
Filler selection	Stability – physical	3	3	M
Moisture control in manufacturing	*In vivo* performance	1	2	L
Moisture control in manufacturing	Dissolution	1	3	L
Moisture control in manufacturing	Assay	2	4	M
Moisture control in manufacturing	Degradation	4	4	H
Moisture control in manufacturing	Content uniformity	1	1	L
Moisture control in manufacturing	Appearance	1	2	L
Moisture control in manufacturing	Friability	2	2	L
Moisture control in manufacturing	Stability – chemical	3	3	M
Moisture control in manufacturing	Stability – physical	2	2	L

Table 3.2.P.2.2-1 Results of PHA (continued)

Hazard	Event	Severity	Probability	Risk score
Blending	*In vivo* performance	2	2	L
Blending	Dissolution	1	2	L
Blending	Assay	3	3	M
Blending	Degradation	1	2	L
Blending	Content uniformity	3	3	M
Blending	Appearance	2	2	L
Blending	Friability	1	2	L
Blending	Stability – chemical	1	2	L
Blending	Stability – physical	1	2	L
Lubrication	*In vivo* performance	3	3	M
Lubrication	Dissolution	3	4	H
Lubrication	Assay	1	2	L
Lubrication	Degradation	1	2	L
Lubrication	Content uniformity	3	3	M
Lubrication	Appearance	2	3	M
Lubrication	Friability	3	3	M
Lubrication	Stability – chemical	1	2	L
Lubrication	Stability – physical	2	2	L
Compression	*In vivo* performance	3	3	M
Compression	Dissolution	3	3	M
Compression	Assay	2	2	L
Compression	Degradation	2	2	L
Compression	Content uniformity	1	2	L
Compression	Appearance	2	4	M
Compression	Friability	2	4	M
Compression	Stability – chemical	1	2	L
Compression	Stability – physical	2	3	M

Table 3.2.P.2.2-1 Results of PHA (continued)

Hazard	Event	Severity	Probability	Risk score
Coating	*In vivo* performance	2	2	L
Coating	Dissolution	2	2	L
Coating	Assay	2	2	L
Coating	Degradation	2	2	L
Coating	Content uniformity	1	1	L
Coating	Appearance	3	3	M
Coating	Friability	2	2	L
Coating	Stability – chemical	1	1	L
Coating	Stability – physical	1	2	L
Packaging	*In vivo* performance	1	1	L
Packaging	Dissolution	1	1	L
Packaging	Assay	1	1	L
Packaging	Degradation	1	1	L
Packaging	Content uniformity	1	1	L
Packaging	Appearance	1	1	L
Packaging	Friability	1	1	L
Packaging	Stability – chemical	3	3	M
Packaging	Stability – physical	3	3	M

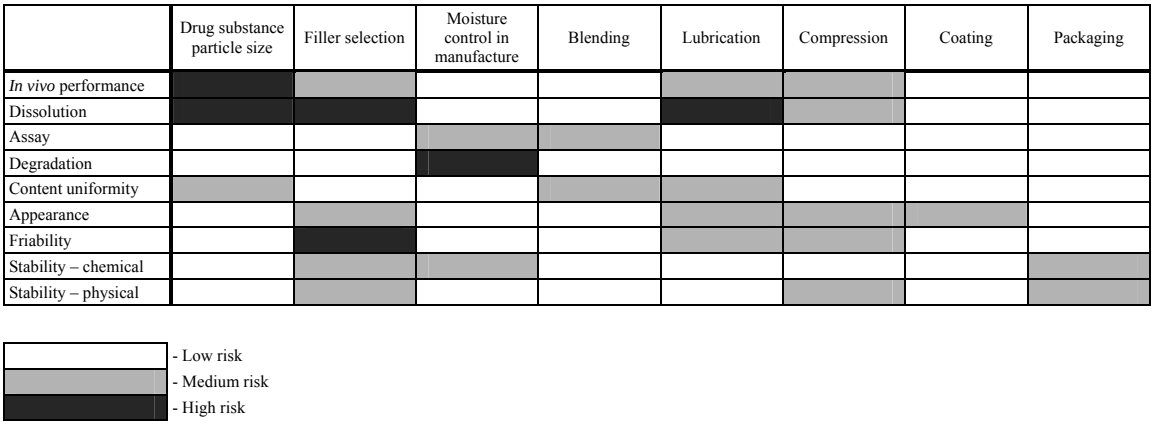


Figure 3.2.P.2.2-3 Summary of Initial Risk Assessment

Drug substance particle size, excipients and water content were assessed as attributes that could affect tablet quality, based on the initial risk assessment before development of the drug product described above. Details of the assessment are shown in Table 3.2.P.2.2-2.

Table 3.2.P.2.2-2 Initial Risk Assessment of Sakura Tablet

Factor	Risk assessment
API	Drug substance particle size could affect *in vivo* performance due to the low solubility and high permeability.
Excipient	Poorly soluble (inorganic) excipients could affect dissolution rate.
	Soluble (organic) excipients could affects compressing property in compression.
	Hydrophobic excipients (lubricants) could affect dissolution rate.
Manufacturing process	API is known to undergo hydrolysis and this will probably preclude aqueous wet granulation processes.
	The blending process must ensure homogeneous 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.

3.2.P.2.3 Manufacturing Process Development

1) Risk Assessment on Drug Product Composition and Manufacturing Process

Risk assessment using Failure Mode Effects Analysis (hereafter FMEA) was performed to establish the drug product composition and its manufacturing process on a commercial scale.

The risk assessment will be performed on factors that are selected based on initial risk assessment results. The product composition and manufacturing process will then be designed.

Among the process inputs identified in the initial risk assessment that affect critical quality attributes, the effects of excipients selection (poorly soluble, soluble) and water content in the granulation process on drug substance quality attributes were deleted from the FMEA risk assessment criteria because the direct compression method was employed.

The initial risk assessment to establish the manufacturing process is likely to indicate that the blending time in the blending process could be a critical process. In addition, selection of direct compression was likely to require compression pressure in the compression process as a critical process. In the FMEA assessment, the effects of batch size on the blending process and the effects of compression speed on the compression process were included as assessment criteria.

The results of the above assessment are shown in Table 3.2.P.2.3-1.

Table 3.2.P.2.3-1 Results of Item Evaluation

Factor	Critical quality attributes identified in the initial risk assessment	Items for the FMEA assessment (critical quality attributes)
Drug substance particle size	*In vivo* performance (solubility)	Dissolution (because amokisinol was confirmed as a BCS class 2 compound)
Excipient selection	Dissolution	Omitted from test items because direct compression was employed.
	Compressibility	
Lubricant amount	Dissolution	Dissolution
Granulation	Water content	Omitted from test items because direct compression was employed.
Blending (blending time)	Content uniformity	Content uniformity
Blending (batch size)	Content uniformity	Content uniformity
Blending (lubricant)	Dissolution	Dissolution
Compression (compression pressure)	Disintegration and dissolution	Dissolution
Compression (compression speed)	Disintegration and dissolution	Dissolution

FMEA assessment, which treats factors listed in the initial risk assessment as failure mode, was performed. For evaluation, scores for severity, probability, and detectability are defined as below. When the value obtained by multiplying the severity, probability and detection timings by the risk priority number (RPN) is <20, the rank is defined as low. When the value is from 20 or more to less than 40, the rank is defined as medium, and when the value is 40 or more, the rank is high.

The risk assessment was evaluated by team members who are responsible for drug product development. The results of the evaluation were discussed and confirmed by the team members. When the ratings among the team members differed, the higher rates were employed.

Table 3.2.P.2.3-2 Definition of Severity

Severity rank	Score	Remarks
Deviation	1	In case which affects the quality significantly, score is 3 or 4.
Passed the re-test	2	———
Sub-batch or rejected batch	3	———
Stop the flow of manufacture	4	Affecting availability of the product
Recall	5	———

Table 3.2.P.2.3-3 Definition of Outbreak Probability

Probability rank	Score	Remarks
≤1/10000	1	Not more than once per 10,000 lots.
1/1000	2	Not more than once per 1,000 lots and not less than once per 10,000 lots
1/100	3	Not more than once per 100 lots and not less than once per 1,000 lots
1/10	4	Not more than once per 10 lots and not less than once per 100 lots
>1/10	5	Not less than once per 10 lots

Table 3.2.P.2.3-4 Definition of detectability

Detectability rank	Score	Remarks
Before each unit operation	1	———
During a unit operation	2	———
During series of unit operations	3	———
Test of the final product	4	———
Found by customers	5	———

The results of the risk analysis on each failure mode based on definitions of FMEA assessment are shown in Figure 3.2.P.2.3-1 and Table 3.2.P.2.3-5.

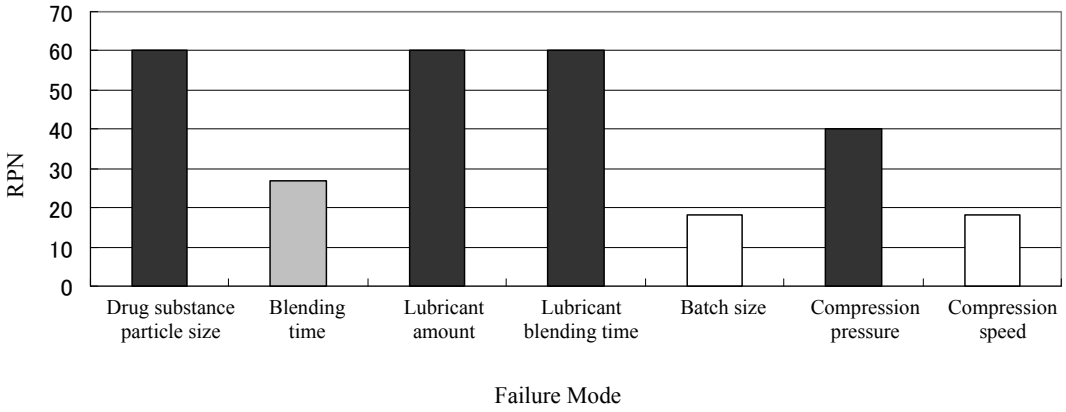


Figure 3.2.P.2.3-1 Results of FMEA Risk Assessment

Table 3.2.P.2.3-5 Results of FMEA Risk Assessment

Target product profile/quality property	Potential failure mode	Effect	Severity	Outbreak probability	Detectability	RPN
Dissolution	Drug substance particle size	Decreased dissolution	3	5	4	60
Content uniformity	Blending time	Not uniform	3	3	3	27
Dissolution	Lubricant amount	Decreased dissolution	3	5	4	60
Dissolution	Lubricant blending time	Decreased dissolution	3	5	4	60
Content uniformity	Batch size	Not uniform	3	2	3	18
Dissolution	Compression pressure	Decreased dissolution	4	5	2	40
Content uniformity	Compression speed	Not uniform	3	2	3	18

Severity	Score
Deviation	1
Passed the re-test	2
Rejection of sub-batch or batch	3
Stop the flow of manufacture	4
Recall	5

Outbreak probability	Score
≤1/10000	1
1/1000	2
1/100	3
1/10	4
>1/10	5

Detectability	Score
Before each unit operation	1
During a unit operation	2
During series of unit operations	3
Test of the final product	4
Found by customers	5

Risk priority number	Rank
≥40	
20≤ <40	
<20	

Based on the above results of risk analysis, the manufacturing process was designed mainly according to the nature of the drug substance particles, lubricant blending condition (lubricant amount, lubricant blending time) and compression pressure, which are process inputs that possibly affect critical quality attributes.

4) Effects on Manufacturing Process Quality

PHA was used to assess the effects of the process inputs, which were identified during the manufacturing process evaluation, on the tablet quality attributes.

Following hazards were listed for the risk analysis.

Material attributes

- Drug substance particle size
- Lubricant amount on tablet surface

Process parameter

- Blending (blending speed and blending time)
- Lubricant blending (blending speed and blending time)
- Compression pressure
- Compression speed
- Batch size

The following items were listed for the event (effect) analysis.

Quality attributes influencing clinical performance

- Dissolution
- Assay
- Content uniformity

Physical quality attributes

- Appearance
- Hardness

For risk assessment using PHA, the severity and probability of risks were rated in a similar manner to the initial risk assessment.

The definition of severity and probability were the same as in the initial risk assessment.

Details of summary of effects and conclusions are shown in Table 3.2.P.2.2-6 and Figure 3.2.P.2.2-2 respectively.

Table 3.2.P.2.2-6 Results of PHA

Hazard	Event (Effect)	Severity	Probability	Risk score
Drug substance particle size	Dissolution	3	5	H
Drug substance particle size	Assay	3	1	L
Drug substance particle size	Content uniformity	3	3	M
Drug substance particle size	Appearance	1	1	L
Drug substance particle size	Hardness	1	2	L
Lubricant amount on tablet surface	Dissolution	3	3	M
Lubricant amount on tablet surface	Assay	1	1	L
Lubricant amount on tablet surface	Content uniformity	2	2	L
Lubricant amount on tablet surface	Appearance	3	3	M
Lubricant amount on tablet surface	Hardness	3	3	M
Blending (speed and time)	Dissolution	1	2	L
Blending (speed and time)	Assay	2	2	L
Blending (speed and time)	Content uniformity	3	3	M
Blending (speed and time)	Appearance	1	2	L
Blending (speed and time)	Hardness	2	2	L
Lubricant blending (speed and time)	Dissolution	3	3	M
Lubricant blending (speed and time)	Assay	2	2	L
Lubricant blending (speed and time)	Content uniformity	1	1	L
Lubricant blending (speed and time)	Appearance	2	2	L
Lubricant blending (speed and time)	Hardness	2	2	L
Compression pressure	Dissolution	3	3	M
Compression pressure	Assay	2	2	L
Compression pressure	Content uniformity	2	2	L
Compression pressure	Appearance	2	4	M
Compression pressure	Hardness	3	4	H
Compression speed	Dissolution	2	2	L
Compression speed	Assay	2	2	L
Compression speed	Content uniformity	1	1	L
Compression speed	Appearance	2	2	L
Compression speed	Hardness	2	2	L
Batch size	Dissolution	1	1	L
Batch size	Assay	1	1	L
Batch size	Content uniformity	2	2	L
Batch size	Appearance	1	1	L
Batch size	Hardness	1	1	L

	Quality attributes influencing clinical performance			**Physical quality attributes**	
	Dissolution	Assay	Content uniformity	Appearance	Hardness
Material characteristics					
Drug substance particle size					
Lubricant amount on tablet surface					
Process parameters					
Blending (speed and time)					
Lubricant (blending speed and time)					
Compression pressure					
Compression speed					
Batch size					

Low risk
Medium risk
High risk

Figure 3.2.P.2.2-2 Summary of Effects of Each Parameter on Quality Attributes

Based on the above summary, it was concluded that it was highly likely that the drug substance particle size affects dissolution, and that compression pressure affects tablet hardness. However it is considered that appropriate tablet quality attributes can be maintained by controlling the compression pressure in the manufacturing because the results of an *in vivo* study showed a low effect of the compression pressure on the tablet quality.

5) Risk Assessment after Development of the Manufacturing Process

The results of the risk assessment using FMEA on the manufacturing process in the planned commercial scale after development of the manufacturing process are shown in Figure 3.2.P.2.3-3 and Table 3.2.P.2.3-7. The definitions of severity, probability and detectability follow section 1) described above.

The lubricant amount and lubricant blending time at the risks of the failure mode were judged as low based on the results of design evaluation of the lubricant blending process. In addition, for the compression pressure, the control range was determined and its risk could be decreased. Regarding the blending time, however, its risk was judged as medium both of before and after development of the manufacturing process, because it was found that the blending process needed to be monitored in the control strategy according to the results of design evaluation of the blending process.

The blending process and compression process, which were judged to contain failure mode of medium risk in the risk assessment after assessment of the manufacturing process, were judged as critical processes.

In this direction, the risk concerning drug substance particle size remains high also after the manufacturing process development, because control is required at the acceptance step.

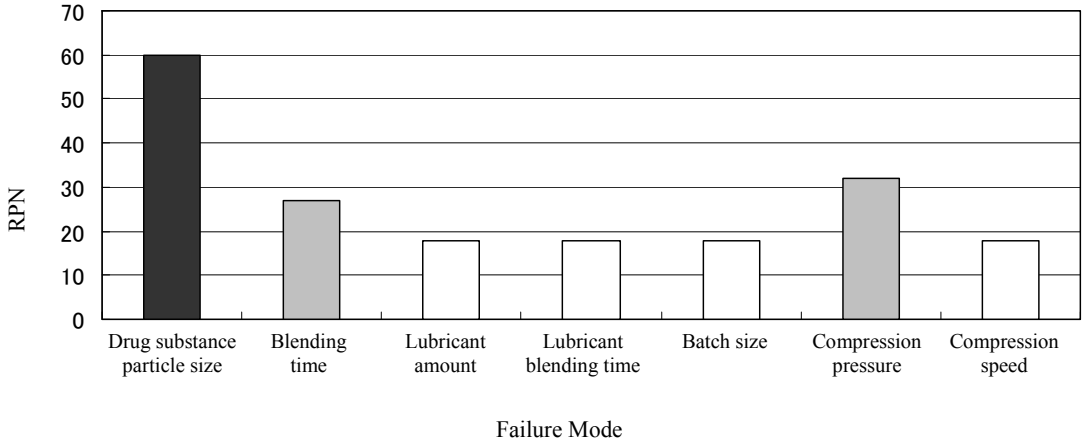


Figure 3.2.P.2.3-3 Results of FMEA Risk Analysis

Table 3.2.P.2.3-7 Results of FMEA Risk Analysis

Target product profile/quality property	Potential failure mode	Effect	Severity	Outbreak probability	Detectability	RPN
Dissolution	Drug substance particle size	Decreased dissolution	3	5	4	60
Content uniformity	Blending time	Not uniform	3	3	3	27
Dissolution	Lubricant amount	Decreased dissolution	3	3	2	18
Dissolution	Lubricant blending time	Decreased dissolution	3	3	2	18
Content uniformity	Batch size	Not uniform	3	2	3	18
Dissolution	Compression pressure	Decreased dissolution	4	4	2	32
Content uniformity	Compression speed	Not uniform	3	2	3	18

Severity	Score
Deviation	1
Passed the re-test	2
Rejection of sub-batch or batch	3
Stop the flow of manufacture	4
Recall	5

Outbreak probability	Score
≤1/10000	1
1/1000	2
1/100	3
1/10	4
>1/10	5

Detectability	Score
Before each unit operation	1
During a unit operation	2
During series of unit operations	3
Test of the final product	4
Found by customers	5

Risk priority number	Rank
≥40	
20≤ <40	
<20	

7) Risk Assessment after Implementation of the Control Strategy

The results of the risk assessment using FMEA after implementation of the control strategy are shown in Figure 3.2.P.2.3-4 and Table 3.2.P.2.3-8. The definitions of severity, probability, and detectability follow the section 1) described above.

The risks of blending time and compression pressure after development of the manufacturing process (before implementing control strategy) were judged as medium. However it was judged that the risks of the blending time and compression pressure decreased because of the use of feedback control using in-line NIR monitoring for the blending, and control using online monitoring for the compression.

In addition, it was judged that risk concerning the drug substance particle size decreased because the design space that contains the particle size was obtained through the drug product design, and the particle size was controlled at the acceptance step.

From these results, the process inputs that affect important quality properties can be managed properly.

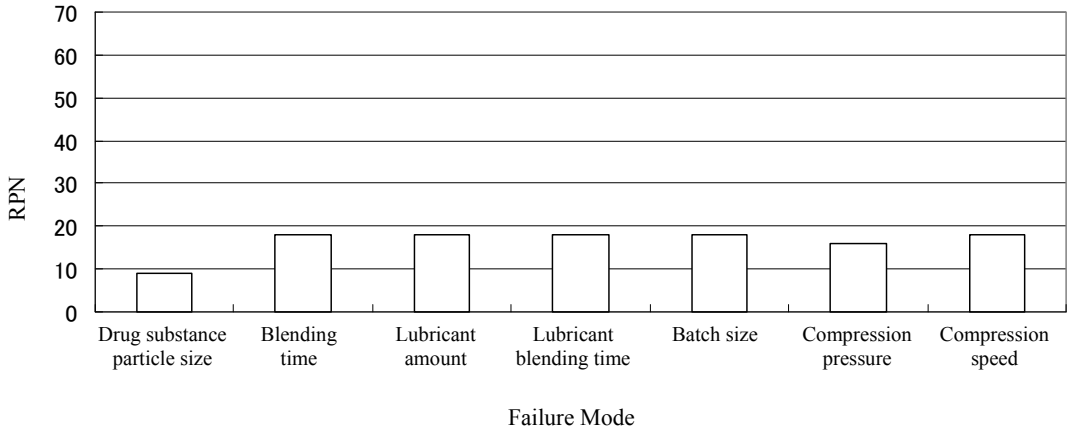


Figure 3.2.P.2.3-4 Results of FMEA Risk Analysis

Table 3.2.P.2.3-8 Results of FMEA Risk Analysis

Target product profile/quality property	Potential failure mode	Effect	Severity	Outbreak probability	Detectability	RPN
Dissolution	Drug substance particle size	Decreased dissolution	3	3	1	9
Content uniformity	Blending time	Not uniform	3	3	2	18
Dissolution	Lubricant amount	Decreased dissolution	3	3	2	18
Dissolution	Lubricant blending time	Decreased dissolution	3	3	2	18
Content uniformity	Batch size	Not uniform	3	3	3	18
Dissolution	Compression pressure	Decreased dissolution	4	2	2	16
Content uniformity	Compression speed	Not uniform	3	2	3	18

Severity	Score
Deviation	1
Passed the re-test	2
Rejection of sub-batch or batch	3
Stop the flow of manufacture	4
Recall	5

Outbreak probability	Score
≤1/10000	1
1/1000	2
1/100	3
1/10	4
>1/10	5

Detectability	Score
Before each unit operation	1
During a unit operation	2
During series of unit operations	3
Test of the final product	4
Found by customers	5

Risk priority number	Rank
≥40	
20≤ <40	
<20	