Based on the above results, the RPNs from the FMEA for the p-CMA are shown in Figure 2.3.P.2.3-11 and Table 2.3.P.2.3-3, where the MAs with a high risk or medium risk were defined as CMA. Therefore, CMAs for each CQA were as follows:

Assay:	Uncoated tablet weight
Uniformity of dosage units:	Granule segregation, uncoated tablet weight, and tablet weight variation
Dissolution:	Drug substance particle size, granule particle size, and uncoated tablet hardness.

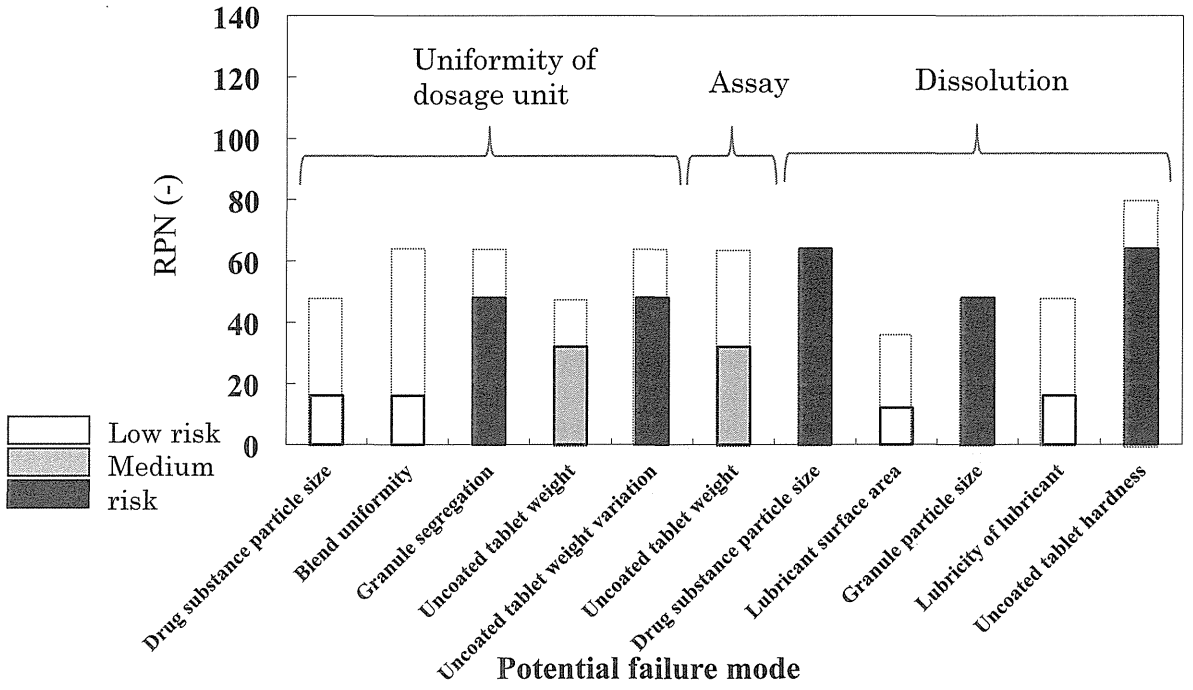


Figure 2.3.P.2.3-11 Results of FMEA risk assessment after manufacturing process development of Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment.

Table 2.3.P.2.3-3 Results of FMEA risk assessment after manufacturing process development of Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	Potential failure mode	Effect	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Drug substance particle size	Not uniform	1	4	4	16
	Blend uniformity	Not uniform	4	1	4	16
	Granule segregation	Not uniform	4	3	4	48
	Uncoated tablet weight	Not uniform	4	2	4	32
	Uncoated tablet weight variation	Not uniform	4	3	4	48
Assay	Uncoated tablet weight	Change in content	4	2	4	32
Dissolution	Drug substance particle size	Change in dissolution	4	4	4	64
	Lubricant surface area	Change in dissolution	1	3	4	12
	Granule particle size	Change in dissolution	3	4	4	48
	Lubricity of lubricant	Change in dissolution	1	4	4	16
	Uncoated tablet hardness	Change in dissolution	4	4	4	64

a) RPN of ≥40 is high risk, ≥20 and <40 is medium risk, and <20 is low risk.

Note: the values which were changed following the manufacturing process development are highlighted in gray.

2.3.P.2.3.3 Determination of CPPs affecting each CMA

2.3.P.2.3.3.1 Extraction of potential CPPs (p-CPPs)

Table 2.3.P.2.3-4 lists the Process Parameter (PP) that could potentially affect each identified CMA of Sakura Bloom Tablets in 2.3.P.2.3.2. Particle size of drug substance is a CMA for dissolution CQA, but the control of particle size of drug substance is performed during the drug substance process, thus it is not described in this section. The uncoated tablet weight is a common CMA for assay and uniformity of dosage units, thus the risk assessment was performed as a CMA for assay.

From the listed process parameters, p-CPPs were identified utilizing the knowledge gained through pharmaceutical development up to the phase III clinical studies (refer to Section 3.2.P.2.3 for details). Identified p-CPPs included inlet air volume, inlet air temperature, spray rate, tableting rotation speed, and compression force. Risk assessment was performed for these p-CPP using FMEA. The details of FMEA are 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 a result, as shown in Figure 2.3.P.2.3-12 and Table 2.3.P.2.3-5, every p-CPP extracted for each CMA was medium risk or high risk. The relation among QTPP, CQA, CMA and p-CPP was summarized in Figure 2.3.P.2.3-13 in the form of an Ishikawa diagram.

Table 2.3.P.2.3-4 Process parameters that can affect CMA

	Factor
Granulation	Spray rate, spray air volume, nozzle size, cap opening, inlet air temperature, exhaust air temperature, inlet air volume, mesh size (bug filter, bottom screen), charged amount, spray gun position, bug filter cleaning(shaking, pulse)
Blending	Blending time, rotation speed, charge-in quantity
Tableting	Compression force (main and pre-compression), tableting rotation speed, rotation speed of power assisted feeder, feeder type

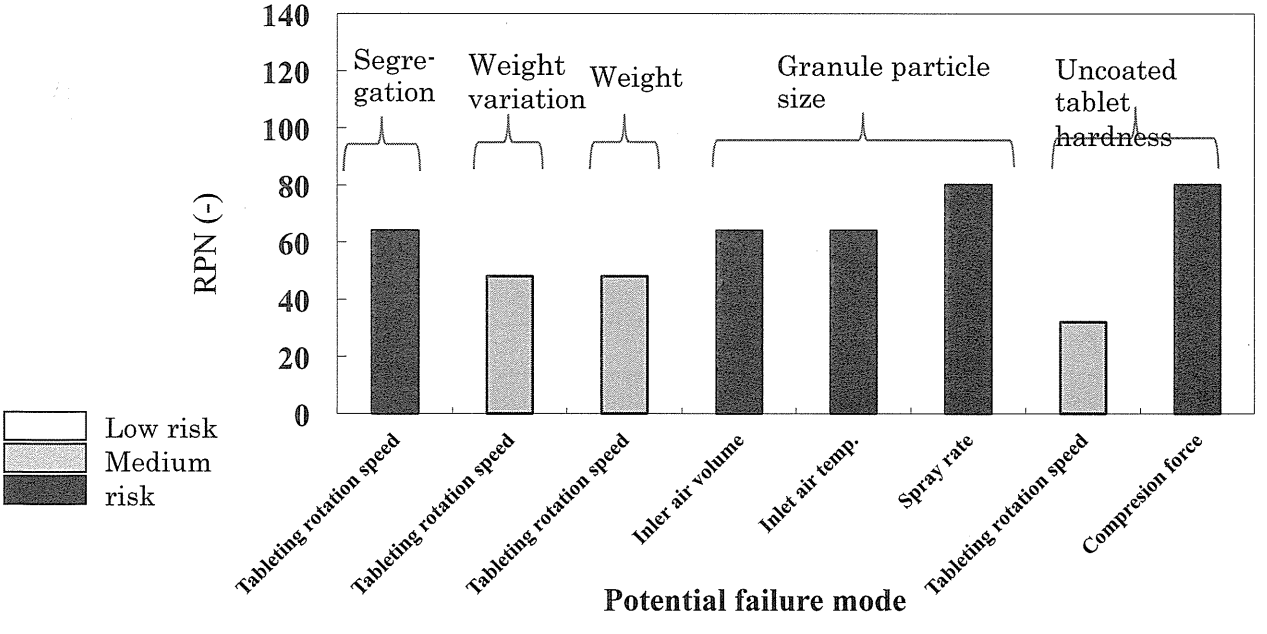


Figure 2.3.P.2.3-12 Results of FMEA risk assessment before manufacturing process development of Sakura Bloom Tablets

Table 2.3.P.2.3-5 Results of FMEA risk assessment before manufacturing process development for Sakura Bloom Tablets
(refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	4	4	64
	Uncoated tablet weight variation	Tableting rotation speed	4	3	4	48
Assay	Uncoated tablet weight	Tableting rotation speed	4	3	4	48
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	4	4	64
		Inlet air temperature	4	4	4	64
		Spray rate	5	4	4	80
	Uncoated tablet hardness	Tableting rotation speed	4	2	4	32
		Compression force	5	4	4	80

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.

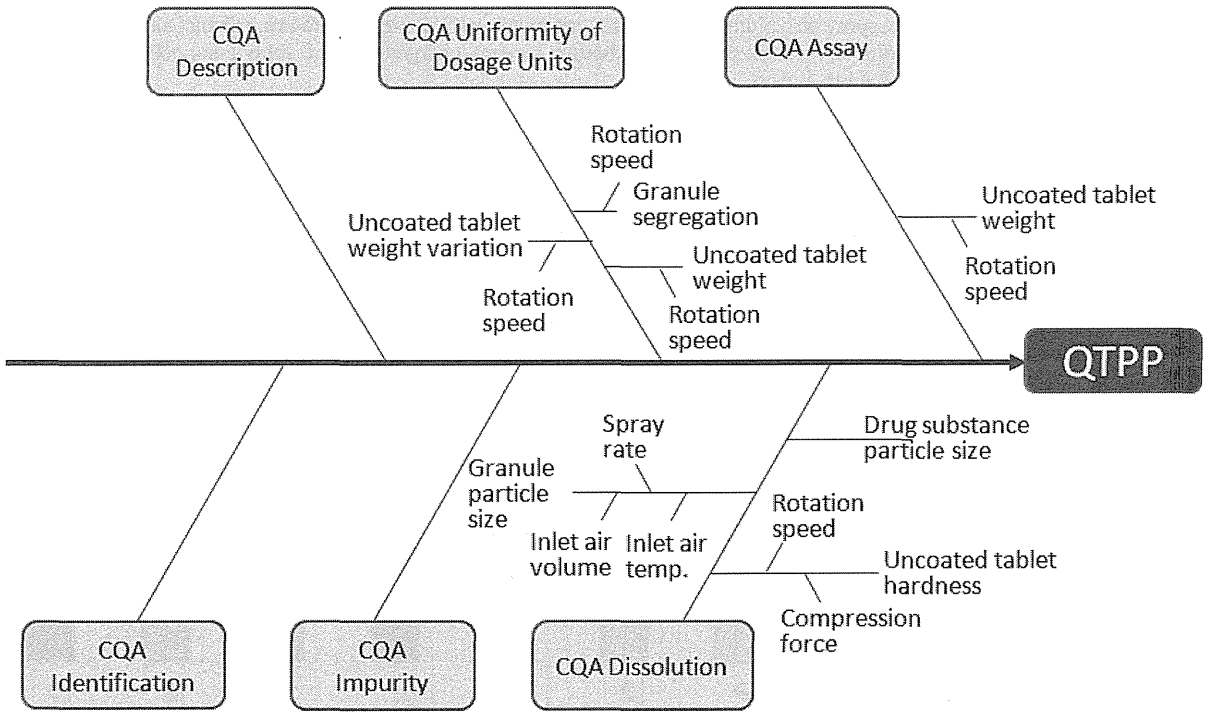


Figure 2.3.P.2.3-13 Relationship between QTPP, CQA, CMA, and p-CPP

2.3.P.2.3.3.2 Identification of CPP

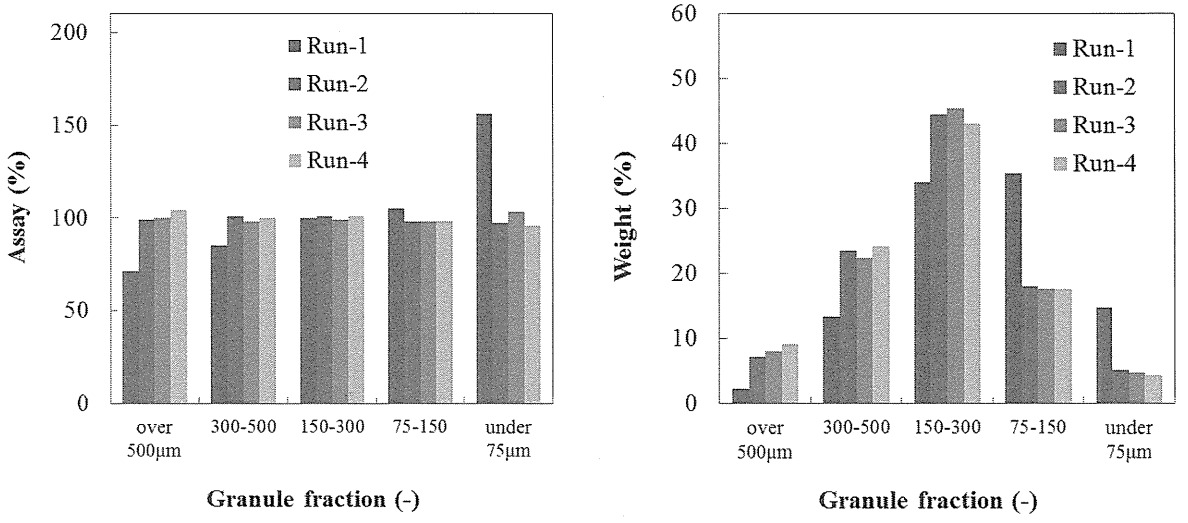
The effect of p-CPPs on CMAs was studied using mainly commercial production equipment.

Effects of tableting rotation speed on granule segregation (CMA)

Upon assessing the affect of tableting rotation speed on granule segregation (CMA), the affects of inlet air volume/inlet air temperature/spray rate on drug substance content of granules by particle size were assessed. Before investigation on a commercial scale, the effects of these variable factors on drug substance content in each fraction were assessed by laboratory scale experiments. As a result, the lower the water content in the granules as a result of the manufacturing conditions (high inlet air volume/high inlet air temperature/low spray rate), the smaller the granule particle size was, and the drug substance content in each fraction tended to be non-uniform. Then, fluid bed granulation was performed using a commercial scale fluid bed granulating machine, according to the design of experiments with L4 (2^3) orthogonal system shown in Table 2.3.P.2.3-6. As shown in Figure 2.3.P.2.3-14, under the manufacturing condition of Run-1, where low water content of granules was expected, the particle size was small and the drug substance content in each fraction was non-uniform, and the risk of segregation may be high as is the case in the laboratory scale experiments. Under the other conditions (Run-2 to Run-4), it was confirmed that granules with a uniform content were obtained regardless of the granule particle size.

Table 2.3.P.2.3-6 Design of experiments with L4 (2^3) orthogonal system

Run	Inlet air volume(m^3/min)	Inlet air temperature(°C)	Spray rate(g/min)
1	50	90	800
2	35	90	1200
3	50	70	1200
4	35	70	800



(a) Content of drug substance by granule particle size (b) Distribution of granulation granules

Figure 2.3.P.2.3-14 Drug substance content in each fraction of granules manufactured at commercial scale

The effects of tableting rotation speed on granule segregation (CMA) were studied on a tableting machine to be used for commercial production, using granules prepared by blending the granules produced above with lubricant. To remove the effects of weight variation, the content of the tablets was adjusted to the weight of a target tablet. As shown in Figure 2.3.P.2.3-15, uniformity was poorer for tablets produced from granules with a high risk of segregation (Run-1) at a rotation speed of 50 rpm of the tableting machine. Therefore, the severity risk score was not decreased, although the probability risk score, for affect of tableting rotation speed on granule segregation (CMA), was decreased.

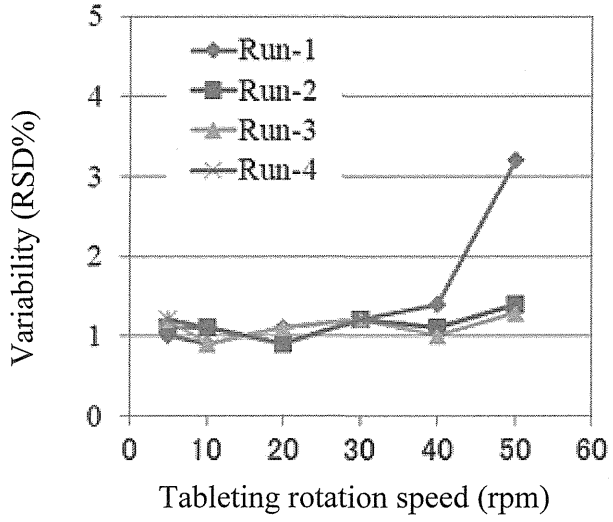


Figure 2.3.P.2.3-15 Relationship between tableting rotation speed and content variation

The affect of tableting rotation speed on the CMA of uncoated tablet weight variation was assessed using granules for tableting shown in Figure 2.3.P.2.3-14. As a result, as shown in 2.3.P.2.3-16, the tableting rotation speed did not affect weight variation in any granules for tableting. Also, the uncoated tablet weight was not affected by the rotation speed. Therefore, it was found that the severity risk score of the effects of a rotation speed on CMA uncoated tablet weight/uncoated tablet weight variation was low.

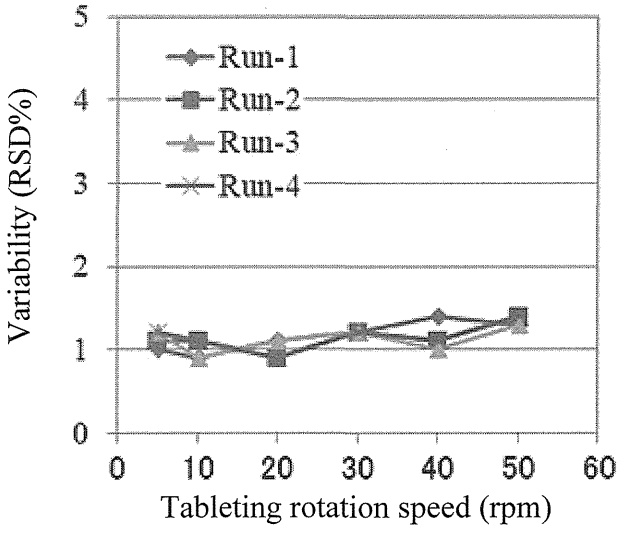


Figure 2.3.P.2.3-16 Relationship between tableting rotation speed and weight variation

Effects of inlet air volume/inlet air temperature/spray rate on CMA granule particle size

The affect of inlet air volume/inlet air temperature/spray rate in fluid bed granulation on granule particle size was assessed. Fluid bed granulation was performed at a production scale, based on the DoE with L4 (2^3) orthogonal system shown in Table 2.3.P.2.3-6. The particle size of the granules produced was analyzed with multiple linear regressions, and the affect of each parameter on the granule particle size were examined. As shown in Figure 2.3.P.2.3-17 and 2.3.P.2.3-18, all 3 factors affected the granule particle size, and spray rate had the greatest effect. Therefore, only the probability risk score in which inlet air volume/inlet air temperature affects the granule particle size was decreased, and the risk score of spray rate was not reduced.

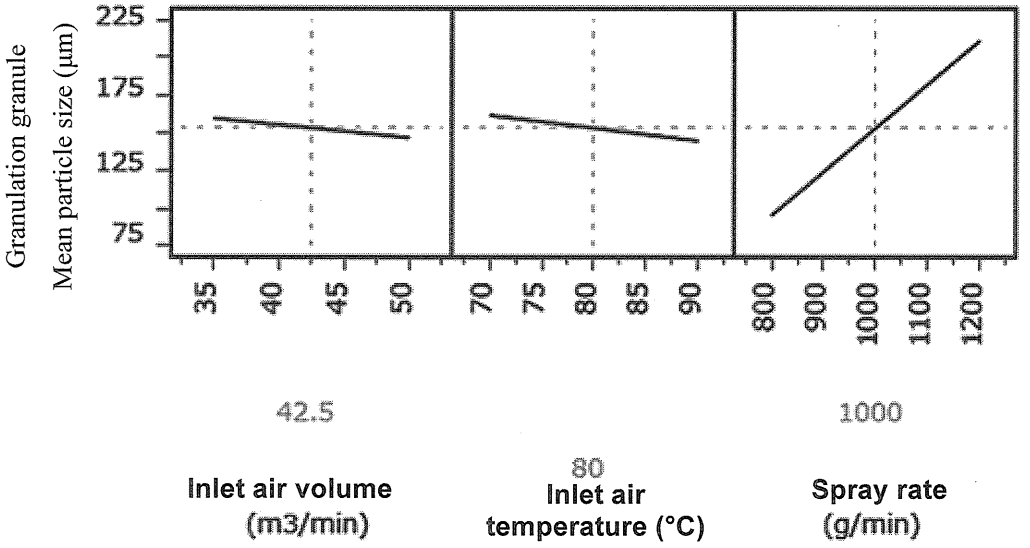


Figure 2.3.P.2.3-17 Effects of each process parameter on granule particle size

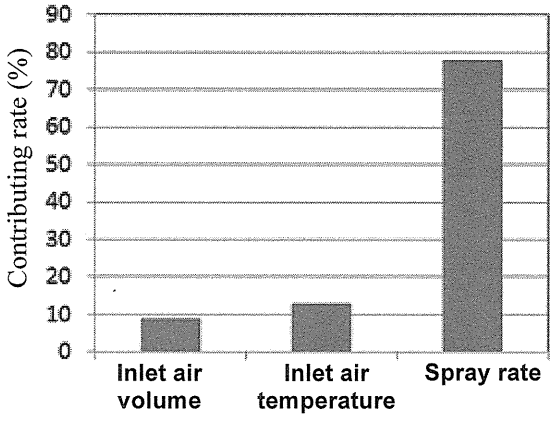


Figure 2.3.P.2.3-18 Contributing rate of each parameter on granule particle size

Effects of tableting rotation speed/Compression force on CMA uncoated tablet hardness

The affect of tableting rotation speed/compression force on the CMA uncoated tablet hardness was assessed using Run-2 granules shown in Figure 2.3.P.2.3-14. As a result, as shown in Figure 2.3.P.2.3-19, the tableting rotation speed did not affect the uncoated tablet hardness, but the compression force did. Even in the case of tableting at different rotation speeds, the rotation speeds used did not affect the compression force on hardness of the tablets, and no interaction was found between them, thus, only the compression force should be considered for the uncoated tablet hardness. Therefore, the risk score of the significance of the effects on uncoated tablet hardness was found to be low in terms of rotation speed, but not decreased in terms of compression force.

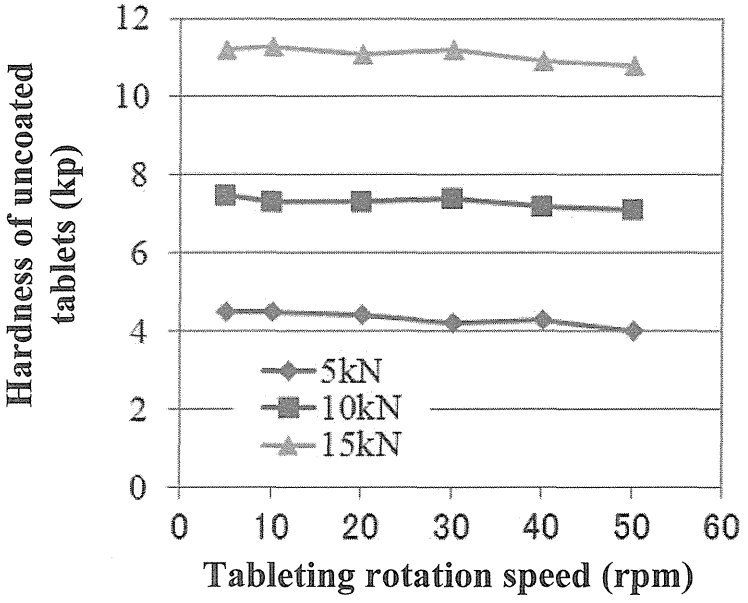


Figure 2.3.P.2.3-19 Effects of tableting rotation speed/compression force on uncoated tablet hardness

Based on the above results, the risk assessment after process development and the RPNs from the FMEA for p-CPP is shown in Figure 2.3.P.2.3-20 and Table 2.3.P.2.3-7. Here, the PPs with medium risk or high risk were defined as CPP. Therefore, the CPPs for each CMA were as follows.

Granule segregation:	Tableting rotation speed
(Uncoated tablet weight variation)	
(Uncoated tablet weight)	
Granule particle size:	Inlet air volume, inlet air temperature, spray rate
Uncoated tablet hardness:	Compression force

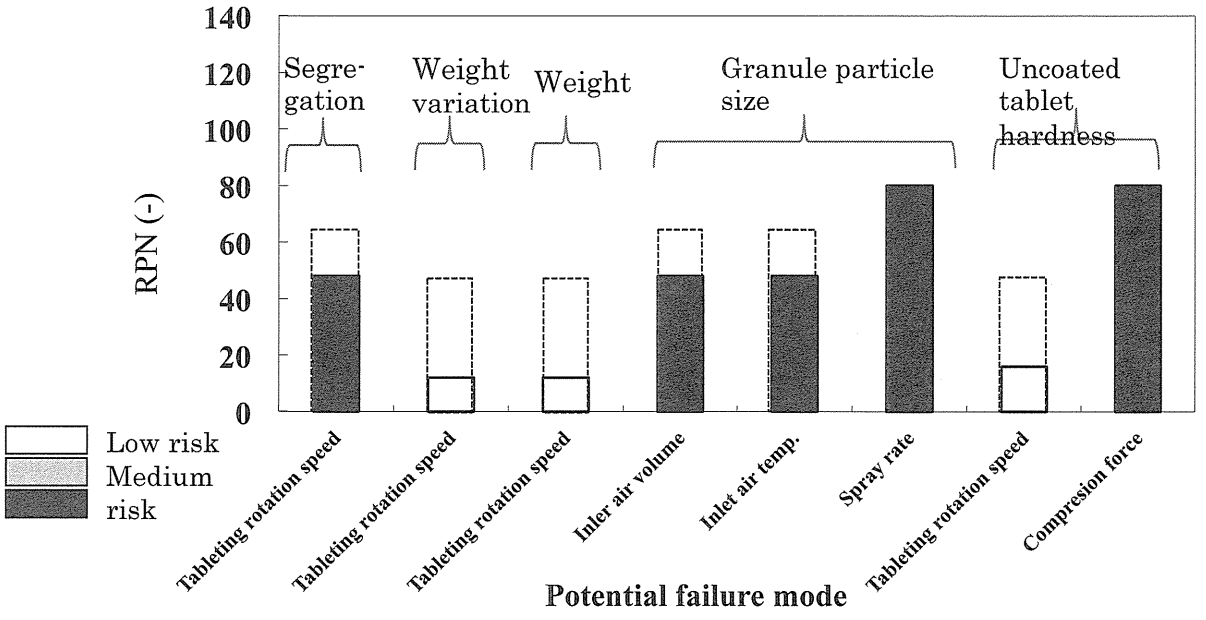


Figure 2.3.P.2.3-20 Results of FMEA risk assessment after manufacturing process development for Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment..

Table 2.3.P.2.3-7 Results of FMEA risk assessment after manufacturing process development for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	3	4	48
	Uncoated tablet weight variation	Tableting rotation speed	1	3	4	12
Assay	Uncoated tablet weight	Tableting rotation speed	1	3	4	12
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	3	4	48
		Inlet air temperature	4	3	4	48
		Spray rate	5	4	4	80
	Uncoated tablet hardness	Tableting rotation speed	2	2	4	16
		Compression force	5	4	4	80

a) RPN of ≥40 is high risk, ≥20 and <40 is medium risk, and < 20 is low risk.

Note: where a value was changed following manufacturing process development ishighlighted in gray

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2.3.P.2.3.4 Construction of the control strategy

The relationship between each CMA/CPP, QTPP, and CQA of Sakura Bloom Tablets, which was defined in 2.3.P.2.3.2 and 2.3.P.2.3.3, is summarized in Figure 2.3.P.2.3-21 in the form of an Ishikawa diagram.

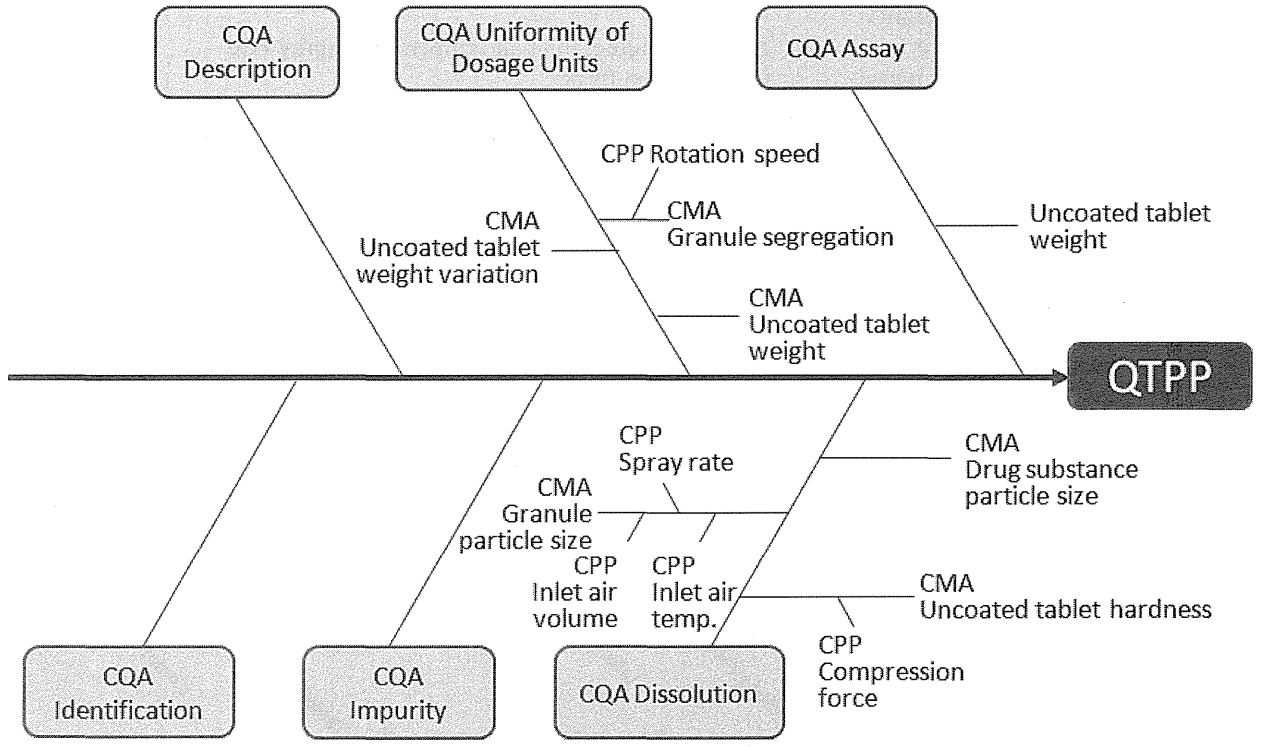

Figure 2.3.P.2.3-21 Relationship between QTPP, CQA, CMA, and CPP

The control strategy to assure each CQA is shown below.

2.3.P.2.3.4.1 uniformity of dosage units (CQA)

For the 3 CMAs affecting uniformity of dosage units (CQA), uncoated tablet weight and uncoated tablet weight variation are determined by in-process control, and granule segregation is monitored by determining drug substance concentrations of the uncoated tablet by an NIR method. If the results exceeded the threshold, PAT feedback control, which controls the rotation speed (CPP) is to be employed. As the drug substance concentration of uncoated tablets is determined in 200 or more tablets per batch, RTRT is to be performed in principle.

2.3.P.2.3.4.2 assay (CQA)

The CMA of uncoated tablet weight which affects assay (CQA) is to be controlled by in-process control. Because Sakura Bloom Tablets specific CPPs are not present, online monitoring control was employed for the compression force of every tablet through the tableting process, as generally performed. A compression force 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 of compression force measured. In addition, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression force control equipment by means of the average weight information periodically measured by automatic sampling, and fed back to the tableting machine by weight control equipment is also used. As is the case in uniformity of dosage units, the drug substance concentration of uncoated tablets is determined in 200 or more tablets; thus, RTRT is to be performed using the mean data in principle.

2.3.P.2.3.4.3 Dissolution (CQA)

The granule particle size is controlled within a certain range in the following ways: 1) Particle size (CMA) of drug substance affecting dissolution (CQA) is a specification item for drug substance, 2) Uncoated tablet hardness (CMA) is controlled by feedback of CPP compression force, 3) Granule particle size (CMA) is monitored using Focused Beam Reflectance Measurement (FBRM), and 4) CPP of spray rate that mostly affects the granule particle size is controlled by PAT feedback.

Regarding uniformity of dosage units and content of drug substance, RTRT is to be performed by determining the drug substance content in uncoated tablets after tableting in principle. On the other hand for dissolution, because a factor controlling CMA covers 2 or more unit processes, feedforward control can be employed from the upstream to the downstream in the manufacturing process. Thus, dissolution prediction formula can be constructed using 3 CMA values, and the dissolution is controlled by establishing design space consisting of these 3 CMA to make feedforward control easy.

Figure 2.3.P.2.3-22 shows the design of experiments performed on a laboratory scale, when preparing the response aspect of dissolution. For experiments, a central composite design was employed.

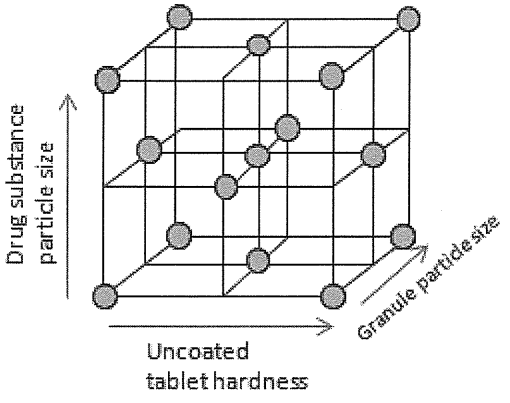

Figure 2.3.P.2.3-22 Dissolution DoE, central composite design

Dissolution test was performed for the drug product manufactured under the conditions allocated by DoE, and the affect of each factor on the dissolution rate were investigated. 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 rate = A – B × particle size of drug substance – C × granule particle size – D × uncoated tablet hardness – E × particle size of drug substance × uncoated tablet hardness

To verify the validity of the formula, each CMA (particle size of drug substance, granule particle size, uncoated tablet hardness; refer to Table 2.3.P.2.3-8) of the formulation produced at pilot scale (20 kg) and at commercial scale (200 kg) was input into the formula, and the predicted values and the actual values were compared. As a result, as shown in Figure 2.3.P.2.3-23, error in prediction, i.e., Root Mean Square Error of Prediction (RMSEP) was 1.6%, showing good agreement. Based on the above results, the formula for dissolution prediction, which was established by DoE at a laboratory scale, was found to be applicable at pilot scale or commercial scale.

Table 2.3.P.2.3-8 Sample for verification of dissolution model

Scale	Particle size of drug substance × 50 (μm)	Granule particle size (μm)	Uncoated tablet hardness (kN)
Pilot (20 kg)	9.8	102	3.9
			7.1
			11.2
	20.2	147	3.8
			7.2
			11.1
	38.9	202	4.0
			7.2
			11.3
Production (200 kg)	10.1	99	3.7
			7.1
			11.1
	19.3	151	3.6
			7.0
			11.0
	19.3	148	3.9
			7.2
			11.4
	40.2	197	3.8
			7.1
			11.2

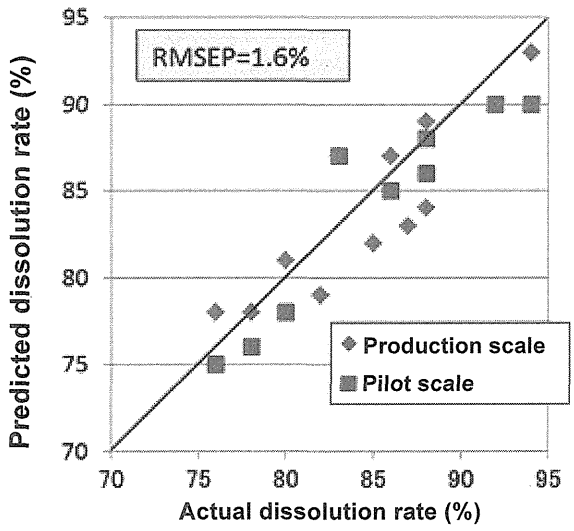

Figure 2.3.P.2.3-23 Fitting verification for the formula of dissolution model

Based on this formula, the response surface is shown in Figure 2.3.P.2.3-24. The cuboid, defines an area that satisfies 80% or more of the dissolution rate (predicted value), specification, was employed to define a design space to assure the dissolution of Sakura Bloom Tablets.
A feedforward control will be used in commercial production to ensure that the dissolution rate is about 90%. In other words, a control to keep the predicted dissolution value constant is established made by appropriately determining the target value for "granule particle size (CMA)" and "uncoated tablet hardness (CMA)" within

this design space, according to the particle size of drug substance obtained in the drug substance process. The overview is shown in Figure 2.3.P.2.3-25.

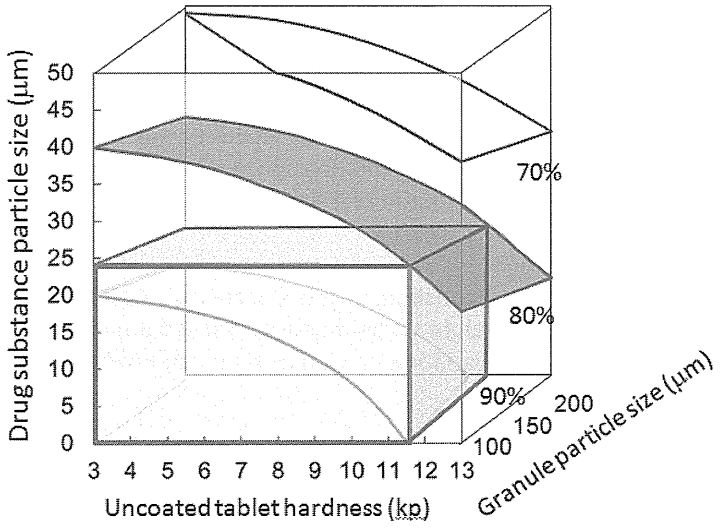

Figure 2.3.P.2.3-24 Design space to assure dissolution CQA (red cuboid)

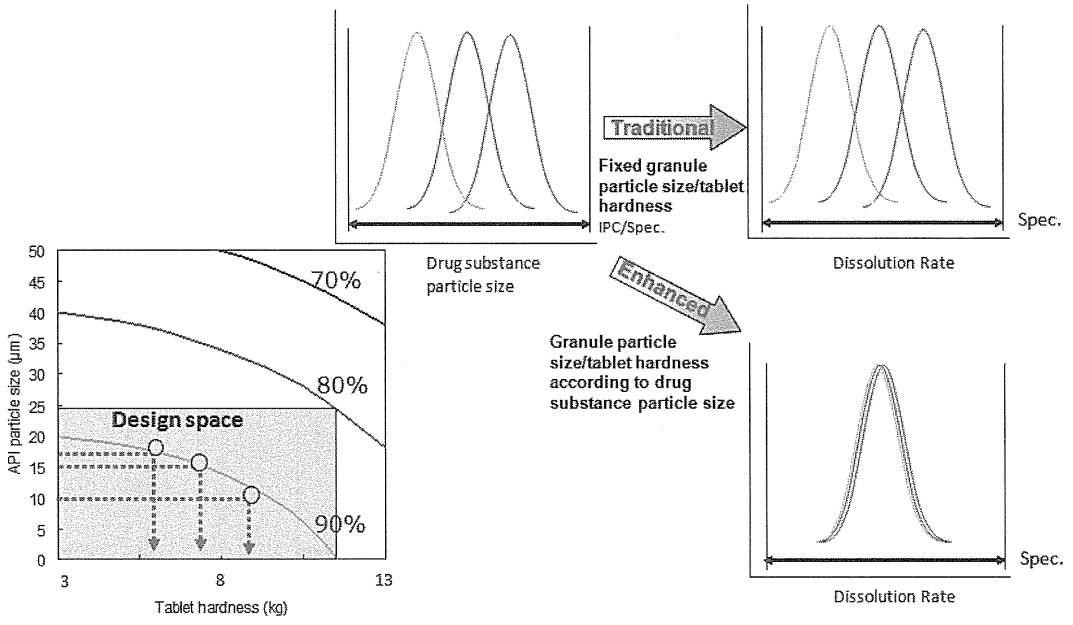

Figure 2.3.P.2.3-25 Overview of feedforward control of dissolution

2.3.P.2.3.4.4 Specifications except for CQA

For identification, it is considered possible to apply an alternative test, by applying an NIR method as an in-process control in the inspection process, and by using a discriminating model constructed by a spectrum in the wavenumber domain indicating the specific peaks of the drug substance. Furthermore, for the description (appearance) it is also considered possible to apply an alternative test as an in-process control in the inspection process.

2.3.P.2.3.5 Review of the risk assessment after implementation of the control strategy

By applying the above control strategy, the risk of each CMA (Figure 2.3.P.2.3-26, Table 2.3.P-2.3-9) and CPP (Figure 2.3.P.2.3-27, Table 2.3.P-2.3-10) was as follows, and all CMA/CPPs were found to be low risk.

2.3.P.2.3.5.1 Risk assessment of CMA

Granule segregation

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for the tableting rotation speed (CPP), by measuring the content of uncoated tablets with an NIR method during tableting in real time, with a feedback loop to the CPP tableting rotation speed.

Uncoated tablet weight/weight variation

The detectability was improved by establishing in-process control. Although the tableting rotation speed affected the uncoated tablet weight/weight variation during the laboratory scale test, rotation speed did not affect uncoated tablet weight/weight variation using a commercial production machine, resulting the risk score of probability decreasing.

Particle size of drug substance

As shown in Section 2.3.S.2, the risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for rotation speed of milling and setting a specification for particle size of the drug substance.

Granule particle size

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for spray rate (CPP), by measuring the granule particle size at granulation in real time, with the feedback loop to CPP spray rate, and by defining a design space including granule particle size.

Uncoated tablet hardness

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for compression force (CPP), with the feedback loop to CPP compression force during tableting in real time, and by defining a design space including uncoated tablet hardness.

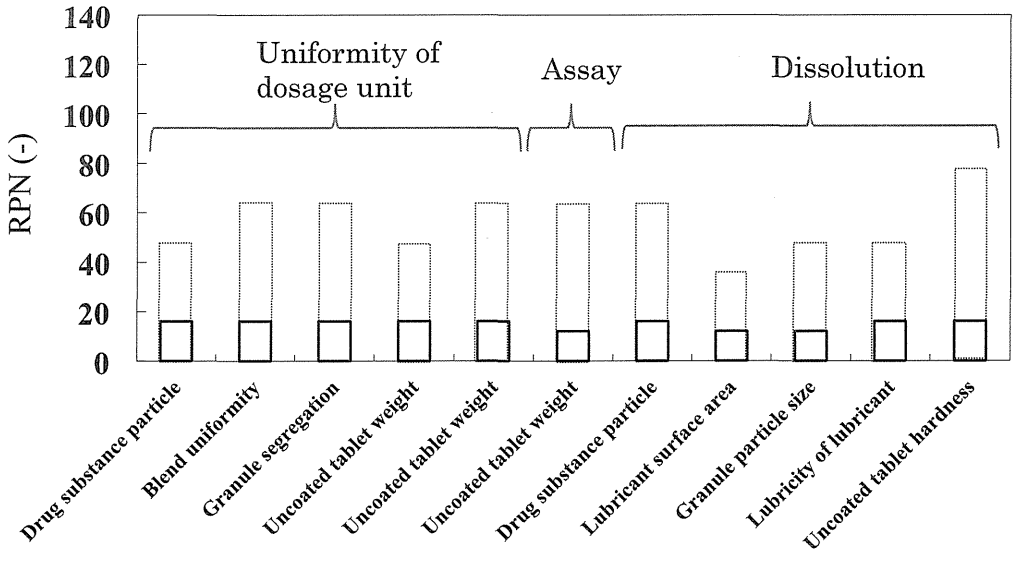

Figure 2.3.P.2.3-26 Results of FMEA risk assessment after applying CMA control strategy for Sakura Bloom Tablets

Note: A dotted line rectangle represents the results of FMEA risk assessment before manufacturing process development.

Table 2.3.P.2.3-9 Results of FMEA risk assessment after applying CMA control strategy for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	Potential failure mode	Effect	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Particle size of drug substance	Not uniform	1	4	4	16
	Blend uniformity	Not uniform	4	1	4	16
	Granule segregation	Not uniform	4	2	2	16
	Uncoated tablet weight	Not uniform	4	1	3	12
	Uncoated tablet weight variation	Not uniform	4	2	2	16
Assay	Uncoated tablet weight	Change in content	4	1	3	12
Dissolution	Particle size of drug substance	Change in dissolution	4	2	2	16
	Lubricant surface area	Change in dissolution	1	3	4	12
	Granule particle size	Change in dissolution	3	2	2	12
	Lubricity of lubricant	Change in dissolution	1	4	4	16
	Uncoated tablet hardness	Change in dissolution	4	2	2	16

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.
Note: the places where a value was changed after applying control strategy were highlighted with a gray color.

2.3.P.2.3.5.2 Risk assessment of CPP

Tableting rotation speed

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the content of uncoated tablets with an NIR method, and using the feedback loop to CPP tableting rotation speed.

Inlet air volume

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Inlet air temperature

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Spray rate

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Compression force

The risk score of robability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and using the feedback loop to the CPP compression force during tableting.

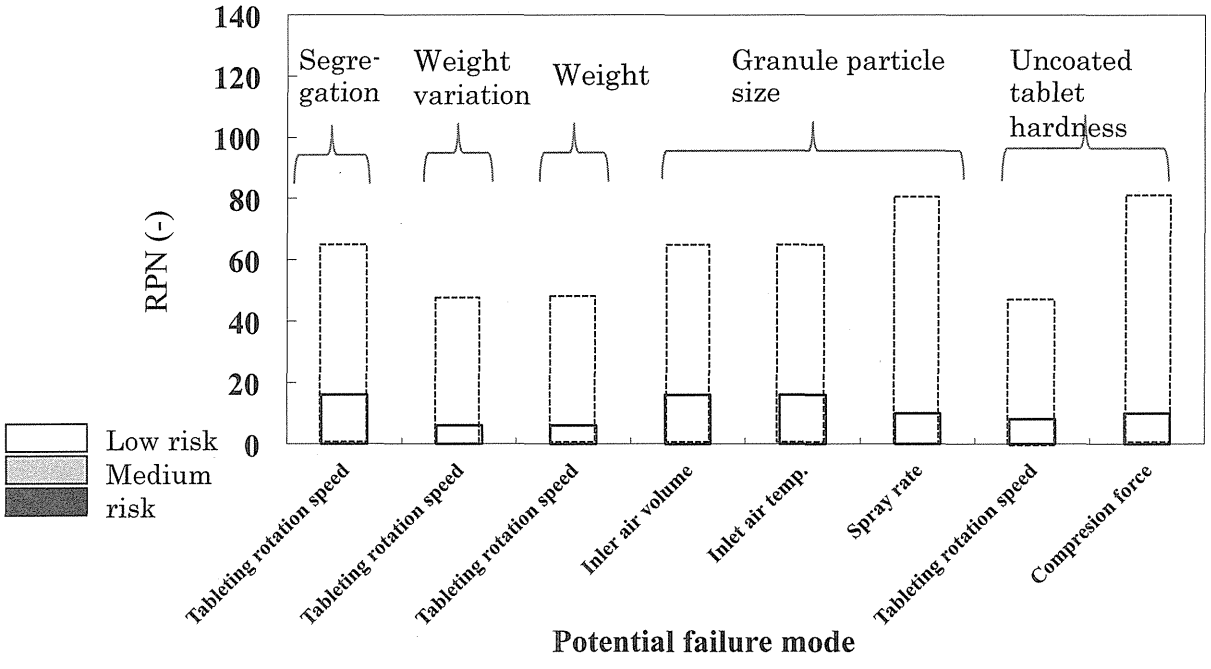

Figure 2.3.P.2.3-27 Results of FMEA risk assessment after applying CPP control strategy for Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment.

Table 2.3.P.2.3-10 Results of FMEA risk assessment after applying CPP control strategy for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	2	2	16
	Uncoated tablet weight variation	Tableting rotation speed	1	2	2	4
Assay	Uncoated tablet weight	Tableting rotation speed	1	2	2	4
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	2	2	16
		Inlet air temperature	4	2	2	16
		Spray rate	5	2	1	10
	Uncoated tablet hardness	Tableting rotation speed	2	1	2	4
		Compression force	5	2	1	10

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.

Note: the columns where a value was changed after applying control strategy are highlighted in gray

2.3.P.2.3.5.3 Overall evaluation of risk assessment

As part of the risk assessment after applying the control strategy, we verified the items that were considered to be low risk at initial risk assessment (Figure 2.3.P.2.3-2), and for which no more examination was made.

Description and identification

As shown in sections of "2.3.P.5 Control of Drug Product" and "2.3.P.8 Stability," differences in production scale, batch of drug substance, batch of excipients, or manufacturing conditions did not affect the description (appearance) and identification, from the stability test results of clinical tablets and formulations for the NDA (pilot scale) and the results of manufacture in commercial scale production. It was thus concluded that the affect of manufacturing processes on these attributes was minimal and they have a low risk.

Impurity

For impurity, as shown in sections "2.3.P.5 Control of Drug Product" and "2.3.P.8 Stability", related impurities in the drug product were not produced/increased during formulation and storage (including stress testing). It was thus found that the affect of the manufacturing processes on impurity was minimal and they have a low risk.

Uniformity of dosage units and assay

We verified the items that were considered to be low risk at initial risk assessment shown in Figure 2.3.P.2.3-2.

- ✓ To assess the affect of drug substance on content, we examined the content of the drug product having drug substance with different particle sizes, as shown in Figure 2.3.P.2.3-5. As a result, the particle size of drug substance was confirmed not to affect the content.
- ✓ To assess the affect of excipients on uniformity of dosage units and assay, the uniformity of dosage units and assay were examined in the drug products manufactured by DoE at each experimental point. As a result, it was confirmed that there were no differences in uniformity of dosage units and assay at all experimental points. Since the formulations for the NDA, which were prepared with even different batches of excipients, and the manufacturing experience on a commercial scale did not matter, it was confirmed that excipients do not affect the uniformity of dosage units and assay.
- ✓ The affect of the granulation process on uniformity of dosage units and assay was examined. As shown in "2.3.P.2.3.2.2 Identification of CMA" and "2.3.P.2.3.3.2 Identification of CPP," it was found that only inappropriate tableting affects the uniformity of dosage units and assay, under the granulation conditions where the drug substance content in each fraction is non-uniform. Since it is obvious that these risks can be controlled by applying the control strategy shown in Section 2.3.P.2.3.4, they were confirmed to be low risk.
- ✓ With respect to the affect of the blending process on content, the blending process was confirmed to have a low risk, because there was no content reduction such as loss of drug substance in the blending process, in any of the drug products shown in "2.3.P.2.3 Manufacturing Process Development."
- ✓ As for the risk that the coating process affects the uniformity of dosage units and assay, a case was considered where damage or degradation of tablets affects the content in the coating process. However, none of the two cases was observed through the manufacturing experiences, and the coating process was confirmed to have a low risk.

Based on the above results, it was verified that the items that were considered to be low risk in the initial risk assessment, following an overall evaluation of the risk assessment, had a low risk.

2.3.P.2.4 Container Closure System

In a stability test, tablets adsorbed water at a maximum of 3% under the high humidity condition of ≥ 75%RH. Afterwards, packaging/vapour permeation test confirmed that PTP/Al (polypropylene on one side and aluminum foil on the other side) and bottle (polyethylene bottle + plastic cap) packagings could control water adsorption to ≤ 3%. From the results of the stability study and evaluation of the design space, it was estimated that Sakura Bloom Tablets manufactured in the range of the design space and packed in the PTP/Al and bottle was stable for not less than 36 months.

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.

- Prunus has no propensity to promote microbial growth.
- Water and excipients used in drug product manufacturing meet JP.
- Microbial Limit Test JP is performed in every 10 batches.

2.3.P.2.6 Compatibility

Not applicable because the final product is a tablet.

2.3.P.3 Manufacture

2.3.P.3.3 Manufacturing Process and Process Control

Figure 2.3.P.3.3-1 shows the process flow of the drug product manufacturing process in commercial production of Sakura Bloom Tablets. Equipment used for the manufacturing process in commercial production will be identical to or have the same principle as the equipment used at the development stage. The manufacturing processes having CMA and CPP that should be controlled to assure the CQAs shown in "2.3.P.2.3.4 Construction of control strategy," i.e., Process 1 (granulation process) and Process 3 (tableting process) were considered as critical steps.

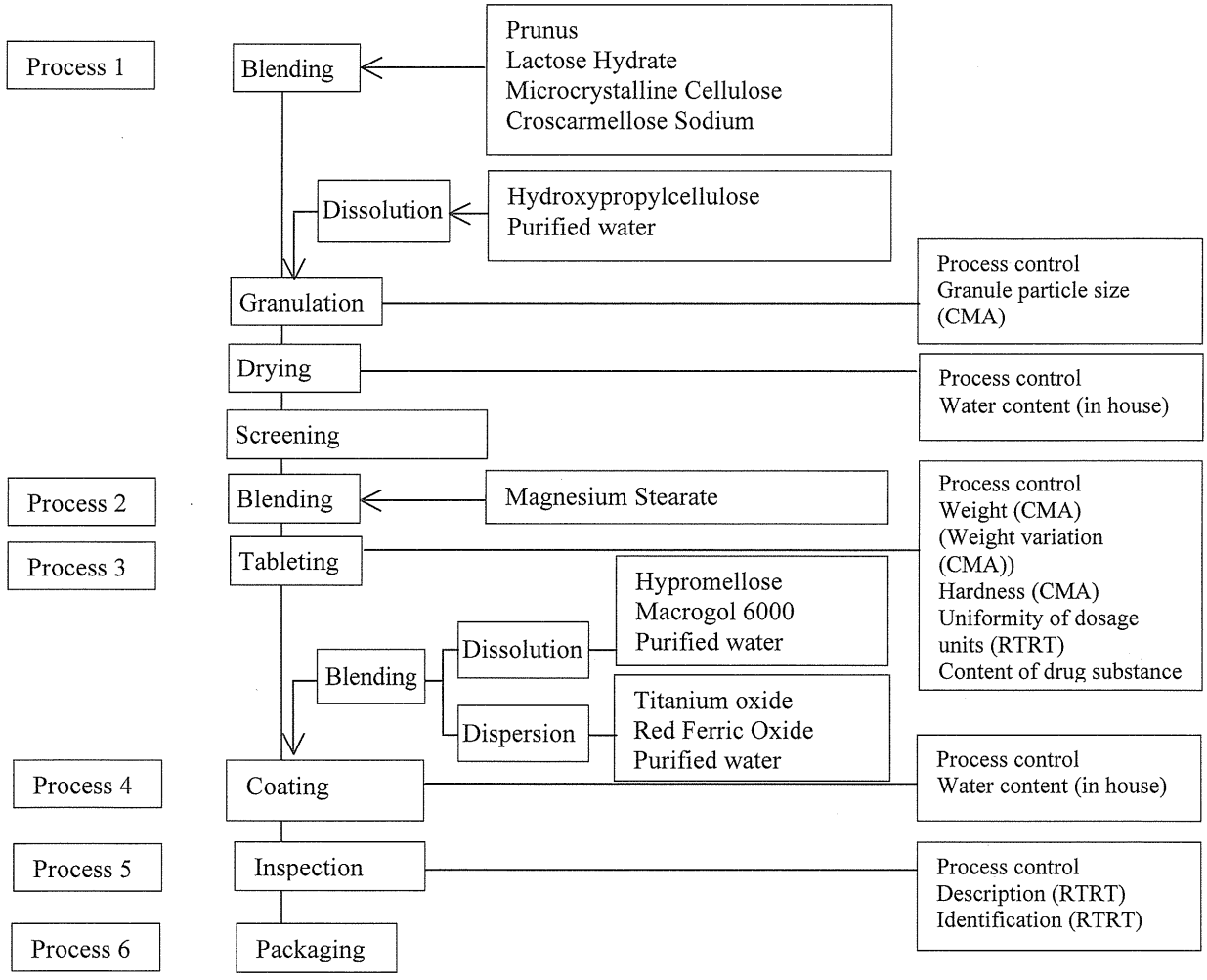

Figure 2.3.P.3.3-1 Overview of manufacturing processes for Sakura Bloom Tablets
<Detail manufacturing process description is omitted in this mock-up>

2.3.P.3.3.1 Manufacturing Parameters and Criteria

Target values/set values in commercial production are shown in Table 2.3.P.3.3-1. These values were set based on the performance assessment conducted by manufacturing of the proposed drug product at pilot scale and commercial scale, and experiences of production in performance qualification. These values will be verified in commercial scale validation and reviewed, as appropriate.

Table 2.3.P.3.3-1 Process parameters of each manufacturing process for Sakura Bloom Tablets and justification
(The reasons in the case of no setting or notification matter) (1/2)

Process	Items	Application Form (Notification matter)	Product master formula etc. (Control range)	Proven Acceptable Range (PAR) and its study scale	Reason/rationale for including in the Application Form or the reason why these are not described in the Application Form.
<Process 1> Granulation process Critical step	Inlet air volume	-	40-45 m^3/min	35-50 m^3/min (Commercial scale)	Inlet air volume is a CPP, but has small effects on CMA granule particle size, and the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to CPP spray rate. Thus, these manufacturing process parameters were not included in the Application Form.
	Inlet air temperature	-	75-85°C	70-90°C (Commercial scale)	Inlet air temperature is a CPP, but has small effects on the CMA granule particle size, and the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to CPP spray rate. Thus, these manufacturing process parameters were not included in the Application Form.
	Spray rate	"900-1100 g/min"	900-1100 g/min	800 to 1200 g/min (Commercial scale)	Spray rate is a CPP and has large effects on the CMA, but the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to the CPP spray rate. Thus, these minor change notification items were included in the Application Form.
<Process 2> Blending Process	Blending time	-	10 minutes	5 to 20 minutes (Commercial scale) 5 to 30 minutes (Pilot scale)	Blending time did not affect the CQA/CMA with a wide range. Therefore, this manufacturing process parameter was not included in the Application Form.
	Rotation speed	-	20 rpm	20 rpm (Commercial scale)	Blending time did not affect the CQA/CMA with a wide range. Therefore, this manufacturing process parameter was not included in the Application Form because it is considered that rotation speed does not affect the CQA/CMA.

- : Not described in the Application Form

Table 2.3.P.3.3-1 Process parameters of each manufacturing process for Sakura Bloom Tablets and justification (The reasons in the case of no setting or notification matter) (2/2)

Process	Items	Application Form (Notification matter)	Product master formula etc. (Control range)	PAR and its study scale	Reason/rationale for including in the Application Form or the reason why these are not described in the Application Form.
<Process 3> Tableting Process Critical step	Tableting Rotation Speed	-	20-30 rpm	5-50 rpm (Commercial scale)	Rotation speed of tableting is a CPP, but has small effects on the CMA uniformity of dosage units and the PAR is assured within a wide range, and the granule segregation (CMA) can be appropriately controlled by feedback control of changing rotation speed in the case of abnormal values of the content of tablets examined by an on-line NIR method during tableting. Thus, these manufacturing process parameters were not included in the Application Form.
	Compression force	"6-14 kN"	6-14 kN	5-15 kN (Commercial scale)	Compression force is a CPP and has large effects on the CMA, but the PAR is assured within a wide range, and Uncoated tablet hardness (CMA) can be appropriately controlled by feedback control to compression force in real time during tableting. Thus, these minor change notification items were included in the Application Form.
<Process 4> Coating process	Inlet air temperature	-	70-80°C	70-80°C (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Inlet air volume	-	40-45 m^3/min	40-45 m^3/min (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Spray rate	-	280-420 g/min	280-420 g/min (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Pan rotation speed	-	2.0-6.0 rpm	2.0-6.0 rpm (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
<Process 5> Inspection process	Omission of description				
<Process 6> Packaging process					

- : Not described in the Application Form