2.3.P.3.3.2 Control Method

Based on the control strategy described in Section 2.3.P.2.3.3, each CQA of assay, uniformity of dosage units, and dissolution, and other specification item CQAs were controlled as shown in Table 2.3.P.3.3-2.

Table 2.3.P.3.3-2 Relationship among CQA and monitoring process and material attributes

CQA	Process	CMA (control item)	Control Method	Control range
Assay	Tableting	Uncoated tablet weight	In-process control	Mean value is within a range of 194 mg ± 3%.
Uniformity of dosage units	Tableting	Uncoated tablet weight variation Granule segregation	In-process control and feedback control of rotation speed of tableting by concentrations of drug substance in uncoated tablets (NIR methods)	Each value is within a range of 90.0% to 110.0%. If the value is out of the range, a feedback control is made.
Dissolution*	(Drug Substance)	(Particle size)	It is controlled in three-dimensional design space so that the dissolution is about 90% (feedback control of spray rate by FBRM, compression force control by compression force controller).	25 μm or less*
	Granulation	Granule particle size		90-210 μm *
	Tableting	Hardness		3-11.5 kp *
Description	Inspection	(Appearance)	Visual observation	-
Identification	Inspection	(Identification)	Identification using an NIR method	-

Process control range of the uncoated tablet weight was set to "the mean mass is within a range of 194 mg ± 3%." To ensure the specification for Assay is met, the range of process control of mass was set to be narrower than that of the specification for Assay, because the specification for Assay is "95.0% to 105.0%."

The range of process control of uniformity of dosage units was set to "each value is within 90% to 110%." Because the specification of uniformity of dosage units is "the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less," the control range of each value was set to be 90% to 110.0%, narrower than 85% to 115.0%. Establishment of the know-how of feedback control in the case of being out of range would make it possible to ensure a good test of uniformity of dosage units. The CMA of uncoated tablet weight variation has been judjed no need to be controlled since the individual tablet assay value calculated by API content in uncoated tablets and the tablet weight is controlled during tableting process.

* With respect to dissolution, as shown in "2.3.P.2.3.4.3 Dissolution (CQA)," RTRT will be performed based on the dissolution prediction formula (shown below) using the parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness.

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

Figure 2.3.P.3.3-2 shows the response surfaces prepared based on this formula. The cuboid consisting of straight lines within an area that satisfies 80% or more of dissolution rate (specification, see 2.3.P.5) was employed as a design space to assure the dissolution of Sakura Bloom Tablets. A feedforward control will be performed as an operation in commercial production so that the dissolution rate is about 90%. In other words, a control to keep the predicted dissolution value being always constant will be made by appropriately determining the target value for a granule particle size and uncoated tablet hardness within this design space according to the particle size of drug substance.
<The design space may be shrinked when the prediction error in the dissolution prediction formula is taken into account.>

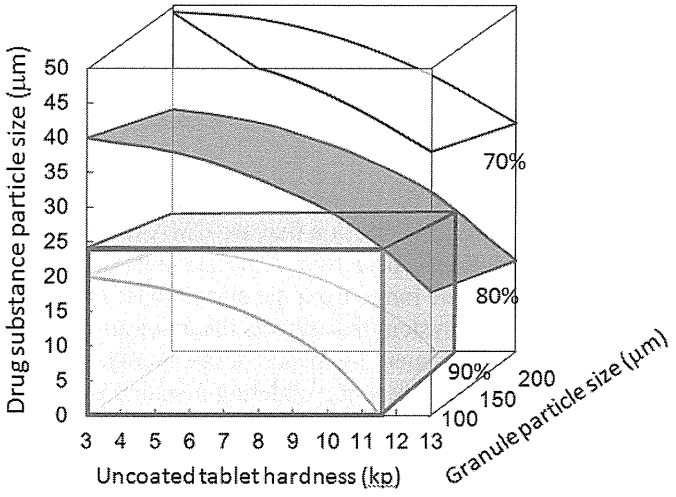


Figure 2.3.P.3.3-2 Response surfaces based on the dissolution prediction formula

2.3.P.3.3.3 Monitoring of Quality Attribute

Based on the control method of Section 2.3.P.3.3.2, quality attributes were to be monitored by the Large-N method, in which content of tablets at tableting is determined with an NIR method, as RTRT of Assay and uniformity of dosage units. For dissolution, RTRT was to be performed based on the dissolution prediction formula, which consists of particle size of drug substance, granule particle size, and uncoated tablet hardness.

2.3.P.3.3.3.1 Granulation process

FBRM was employed as a method to monitor the granule particle size, which is a CMA for dissolution. The measurement conditions of FBRM were assessed by evaluating the position of the sensor and measurement conditions, and the conditions were set as below: Figure 2.3.P.3.3-3 shows the overview.

Equipment: FBRM: C35
Position of the sensor: Side panel of the container of the fluid bed granulator.
Diameter of the measurement probe: φ35 mm
Measurement interval: 5 s

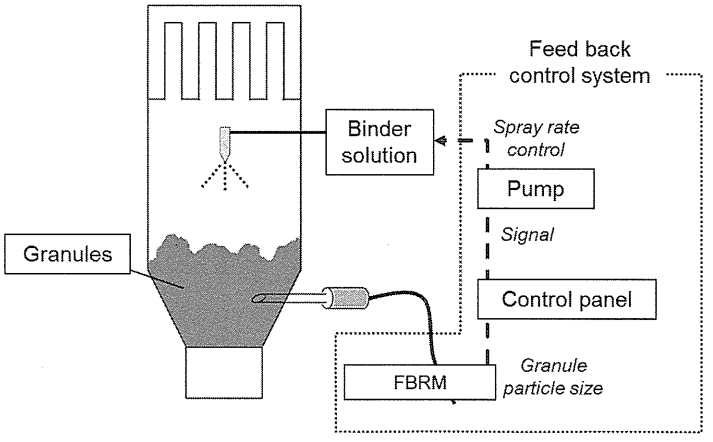


Figure 2.3.P.3.3-3 Overview of the feedback control of fluid bed.

The change in particle size over time during granulation is measured in real time with FBRM, and the spray rate is feedback-controlled to obtain the target particle size of granules after granulation. The target particle size after granulation is established from the obtained particle size of drug substance so that the dissolution rate is about 90%. This target particle size profile is considered ideal. A feedback control is made in real time so that if the particle size is larger than the profile, the spray rate is decreased, and if the particle size is smaller, then the speed is increased.

2.3.P.3.3.3.2 Tableting Process

Online monitoring control was employed for the compression force of each tablet in the tableting process, as control of uncoated tablet weight and weight variation that are CMA for the assay and uniformity of dosage units. 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, was also employed. The overview of feedback is shown in Figure 2.3.P.3.3-4.

For the uncoated tablet weight, which is a CMA for the content, a system is established so that a control is performed if the mean value is out of the range of 194 mg ± 3%.

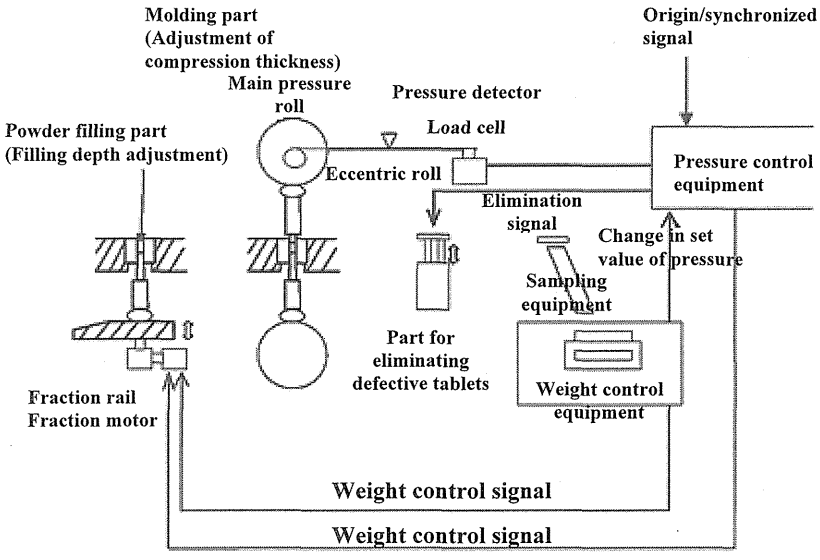


Figure 2.3.P.3.3-4 Overview of the feedback control for tableting weight

For the granule segregation, which is a CMA for uniformity of dosage units, the drug substance concentrations in uncoated tablets were to be monitored with an NIR method, and if the value is over the threshold, PAT feedback control was to be made, which controls the rotation speed (CPP). The drug substance concentrations in uncoated tablets were determined with an on-line NIR method at tableting over time. If each value of drug substance content calculated from the drug substance concentration and tablet weight is out of the range of 90% to 110%, the rotation speed was to be adjusted.

Measuring method: Diffuse transmittance method
Light source: NIR
Detector: InGaAs
Scan: A range of 12,500 to 3,600 cm^{-1}
Number of scans: 64 times
Resolution power: 8 cm^{-1}
Analysis method: Partial Least Squares (PLS) regression analysis

The uncoated tablet hardness, which is a CMA for dissolution, was to be controlled by on-line measurement of the tablets automatically sampled with time in the tableting process. For the uncoated tablet hardness, a target value of a dissolution rate of about 90% was established from the previously obtained particle size of drug substance and the granule particle size, and a system is employed, which feeds back to a tableting machine through a compression force controller.

2.3.P.3.3.3.3 Inspection process

Ten representative samples of film coated tablets after inspection were to be measured for the description (appearance), according to the method described in Table 2.3.P.3.3-3. In a similar way, 3 of the representative samples of film coated tablets after inspection were to be subject to identity testing with an at-line NIR method shown below.

Table 2.3.P.3.3-3 Measurement of description (appearance) by a visual observation method

Measuring method	Sakura Bloom Tablet is taken on a piece of white paper, and the color and shape are observed.
Number of samples	10 tablets

Identification by an at-line NIR method

Measuring method: Diffuse transmittance method
Light source:NIR
Detector: InGaAs
Scan range: 12,500-3,600 cm^{-1}
Number of scans: 64 times
Resolution power: 8 cm^{-1}
Analysis method: Principal Component Analysis (PCA)
Number of samples: 3 tablets

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

Among the specifications, RTRT was employed for the description (appearance), identification, uniformity of dosage units, dissolution and content. The process control methods that serve as each test method are as shown below.

2.3.P.3.4.1 Test items for RTRT

Based on the control strategy described in Section 2.3.P.2.3 Manufacturing Process, description (appearance), identification, uniformity of dosage units, dissolution and assay were considered as possible items for RTRT.

2.3.P.3.4.1.1 Description (appearance) (RTRT)

As RTRT of description (appearance) in the specifications, 10 film-coated tablets after the inspection process were to be tested for description by a visual observation method shown in Table 2.3.P.3.3-3.

2.3.P.3.4.1.2 Identification (RTRT)

As RTRT of identification in the specifications, 3 film-coated tablets after the inspection process were tested for the existence of drug substance, according to (1) at-line NIR method described in Identification (alternative test) <Specifications and Test Methods> in 2.3.P.5.2 Test Methods (Analytical Procedure).

2.3.P.3.4.1.3 Uniformity of dosage units

As RTRT of uniformity of dosage units in the specifications, the drug substance concentrations in uncoated tablets are determined with an on-line NIR method at tableting over time, and the content of drug substance in uncoated tablets is calculated from the drug substance concentration and weight of each tablet. Assessment is

conducted for 200 tablets (10 tablets x 20 time points). Refer to "2.3.P.3.3.3.2 Tableting Process" and "2.3.P.5.6.3.1 Uniformity of Dosage Units (RTRT).

2.3.P.3.4.1.4 Dissolution

The particle size of drug substance is measured as a specification testing in the process of drug substance, by a laser diffraction-scattering type particle size distribution measuring device. Without preparing samples for measurement, the powder of drug substance is measured for particle distribution by the dry method (specification testing of drug substance). Regarding the particle size of the granulation, the particle size at the end of granulation, which is obtained by a FBRM method is used. The uncoated tablet hardness is measured in 200 tablets (10 tablets × 20 time points) sampled over time as described in "2.3.P.3.4.1.3 Uniformity of Dosage Units."
As shown in "2.3.P.2.3.4.3 Dissolution (CQA)," RTRT will be performed based on the dissolution prediction formula using the parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness (formula 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

By controlling each process using this system, dissolution of the drug product is considered to be assured. Therefore, a conventional dissolution test could be omitted.

2.3.P.3.4.1.5 Assay

As RTRT of assay in the specifications, the content of drug substance in uncoated tablets is determined by an on-line NIR method described in "2.3.P.3.4.1.3 Uniformity of Dosage Units," and assessment is made by calculating the mean of 200 tablets.

2.3.P.3.5 Process Validation/Evaluation

For adopted RTRT items, if an unacceptable change in production scale occurred, a RTRT model is re-constructed and re-calibration is carried out. At the stage of NDA filing, assessment was made in a total of 21 batches (refer to Table 2.3.P.2.3-7) manufactured at pilot scale and commercial scale, but process validation using the first 3 batches for commercial production will be performed again.

Quality (CQA) of Sakura Bloom Tablets is ensured by CMAs (composing quality) that are maintained by routine production. The control strategy in production of Sakura Bloom Tablets operates the following maintenance program to verify the model.

Daily check
- Trend analyses of CQA and CMA are performed for every batch produced, and the changes are confirmed to be within an acceptable range.
- If the trend is out of the acceptable level, a comparison is made between the model and conventional testing methods. If the model has some problems, it should be revised. If the model has no problems, the relationship between CPP and CMA is considered to be broken. Thus, control of CPP is reviewed so that CMA has an appropriate value.

Periodical check
- A comparison is made between the values calculated by the model and those obtained by the conventional testing methods at a certain production interval. If the difference between the two is out of the acceptable level, the model should be revised.

Event check
- If raw material or manufacturing equipment is changed, a comparison is made between the values calculated by the model and those obtained by the conventional testing methods under the Pharmaceutical Quality System (PQS). If the difference between the two is out of the acceptable level, the model should be revised.

2.3.P.5 Control of Drug Product

The specifications and test methods for Sakura Bloom Tablets were set based on the results of drug product development, of stability test, and the analytical results of the batches manufactured at pilot scale.

2.3.P.5.1 Specifications and Test Methods

RTRT is employed for description, identification, uniformity of dosage units, dissolution, and assay of the release test items for Sakura Bloom Tablets. Usually, these items for RTRT are used for release tests, and the summary of specifications and test methods is described. In addition, the specifications and test methods of conventional tests by using final drug product are also summarized because of the necessity for the control strategy or stability.

Table 2.3.P.5.1-1 Specifications and test methods for Sakura Bloom Tablets 20 mg

Test items			Test methods	Specification
Description	RTRT Conventional tests	Appearance	The Japanese Pharmacopoeia General Notice	Pale red film-coated tablets
Identification	RTRT		Near infrared absorption spectrometry (NIR method)	Identified as Sakura Bloom Tablet
	Conventional tests	HPLC Retention time	HPLC method	The retention time of the main peak from the sample solution coincides with that of the standard solution.
		Ultraviolet absorption spectrum	Ultraviolet-visible spectrophotometry	The shape of the ultraviolet absorption spectrum from the sample solution coincides with that of the standard solution.
Uniformity of dosage units	RTRT		Near infrared absorption spectrometry (NIR method)	When 200 uncoated tablets, which were sampled to represent the whole batch during the tableting process, are tested for Assay, the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less and that of 75.0% to 125% is 1 or less.
	Conventional tests		Content Uniformity HPLC method	It meets the criteria of the Content Uniformity Test of the Japanese Pharmacopoeia.
Dissolution	RTRT		Calculation by the dissolution model Input parameter • Particle size of drug substance: Laser diffraction particle size distribution analyzer • Granule particle size: FBRM • Uncoated tablet hardness: Tablet hardness tester	The dissolution rate calculated by the dissolution model at the time point of 30 minutes is 80% or higher.
	Conventional tests		Dissolution test (paddle method) Ultraviolet-visible spectrophotometry	Q value in 30 minutes is 80%.
Assay	RTRT		Near infrared absorption spectrometry (NIR method)	The results of the uniformity of dosage units test (RTRT) show a mean of 95.0% to 105.0% of the labeled amount.
	Conventional tests		HPLC method	95.0% to 105.0% of the labeled amount

* According to the Decision Tree, RTRT is usually performed. If RTRT is not available, conventional tests will be performed.

2.3.P.5.2 Test Methods (Analytical Procedures)

Unless otherwise specified, the specifications and test methods for Sakura Bloom Tablets shall apply General Notices, General Rules for Preparations, and General Tests, Processes and Apparatus of the Japanese Pharmacopoeia.

Specifications and test methods for Sakura Bloom Tablets

Describe the information of the Application Form (RTRT & Conventional)

2.3.P.5.2.1 Description

2.3.P.5.2.1.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.1

2.3.P.5.2.1.2 Test methods of conventional tests

<Omitted>

2.3.P.5.2.2 Identification

2.3.P.5.2.2.1 Test methods of RTRT

A discriminating model was used to test the presence of drug substance in film-coated tablets by an at-line NIR method. As shown in Figure 2.3.P.5.2-1, a discriminating model is an approach to make a decision using a library reference prepared by each NIR spectrum of active and placebo tablets. The film-coated tablet tested is judged to be an active tablet if the results are within the threshold of an active tablet. If the test with an at-line NIR method cannot be properly performed, HPLC method is applied. The meaning of "the test cannot be properly performed" is limited to the case where measurement results cannot be obtained due to measuring instruments or a NIR discriminating model.

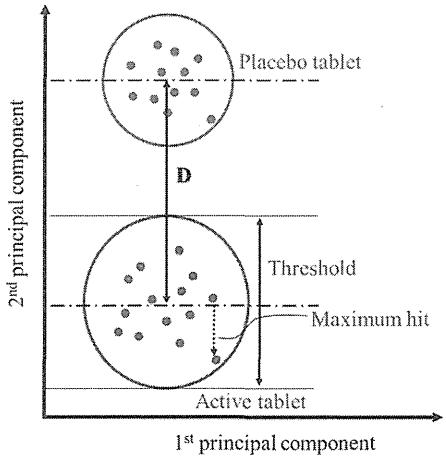


Figure 2.3.P.5.2-1 Overview of a discriminating model

2.3.P.5.2.2.2 Test methods of conventional tests

<Omitted>

2.3.P.5.2.3 Uniformity of dosage units

2.3.P.5.2.3.1 Test methods of RTRT

Refer to Sections 2.3.P.3.3.3.2 and 2.3.P.3.4.1.3.

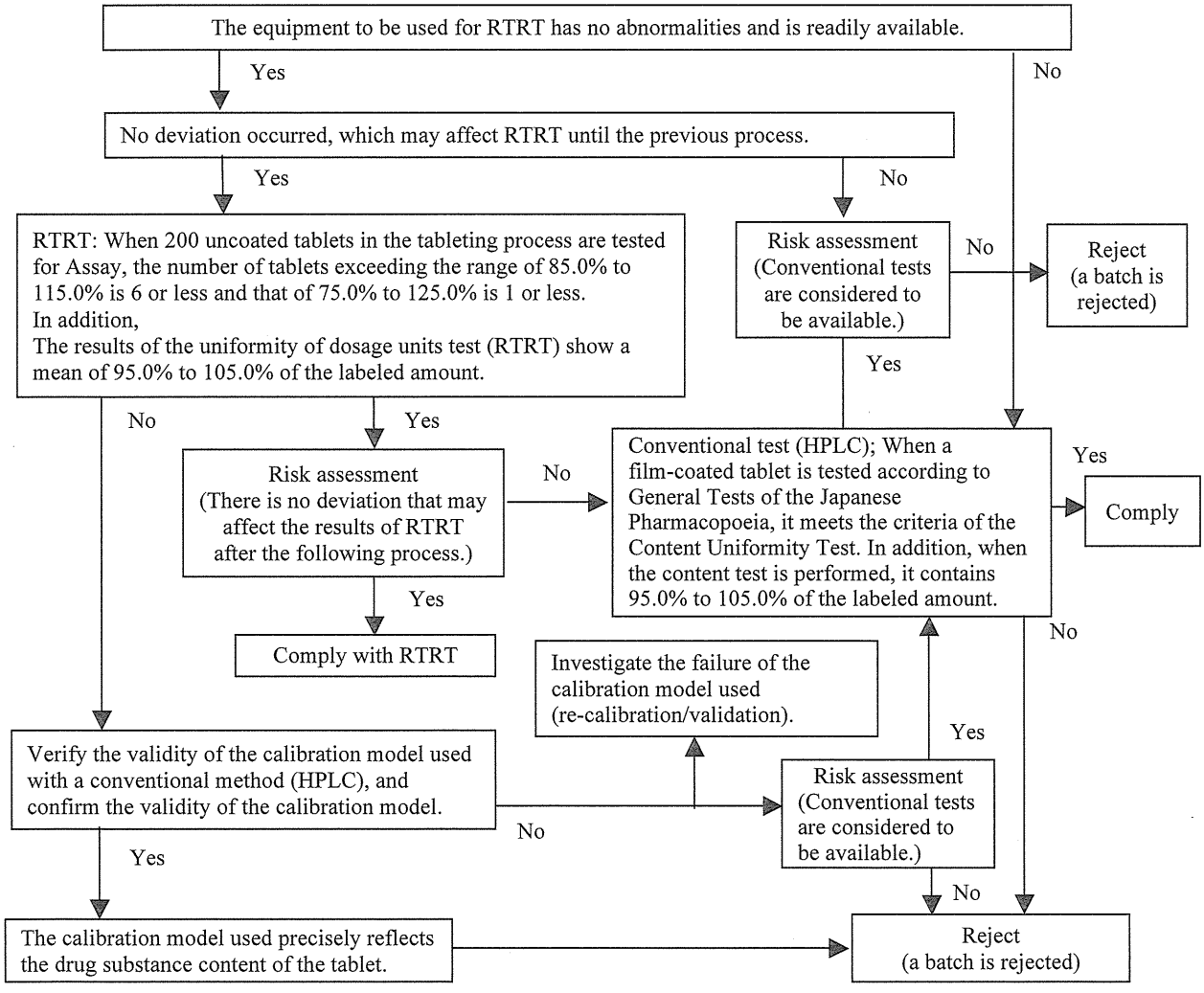
The content of each drug product shall be calculated according to the following formula, using drug substance concentrations of uncoated tablets and the uncoated tablet weight determined by the methods described in 2.3.P.3.3.3.2 Tableting process.

Content of each drug product (%) = drug substance concentrations of uncoated tablets (%) × uncoated tablet weight (mg)/194 (theoretical uncoated tablet weight, mg)

2.3.P.5.2.3.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the following decision tree. This decision tree is the same as that of the Assay.



2.3.P.5.2.4 Dissolution

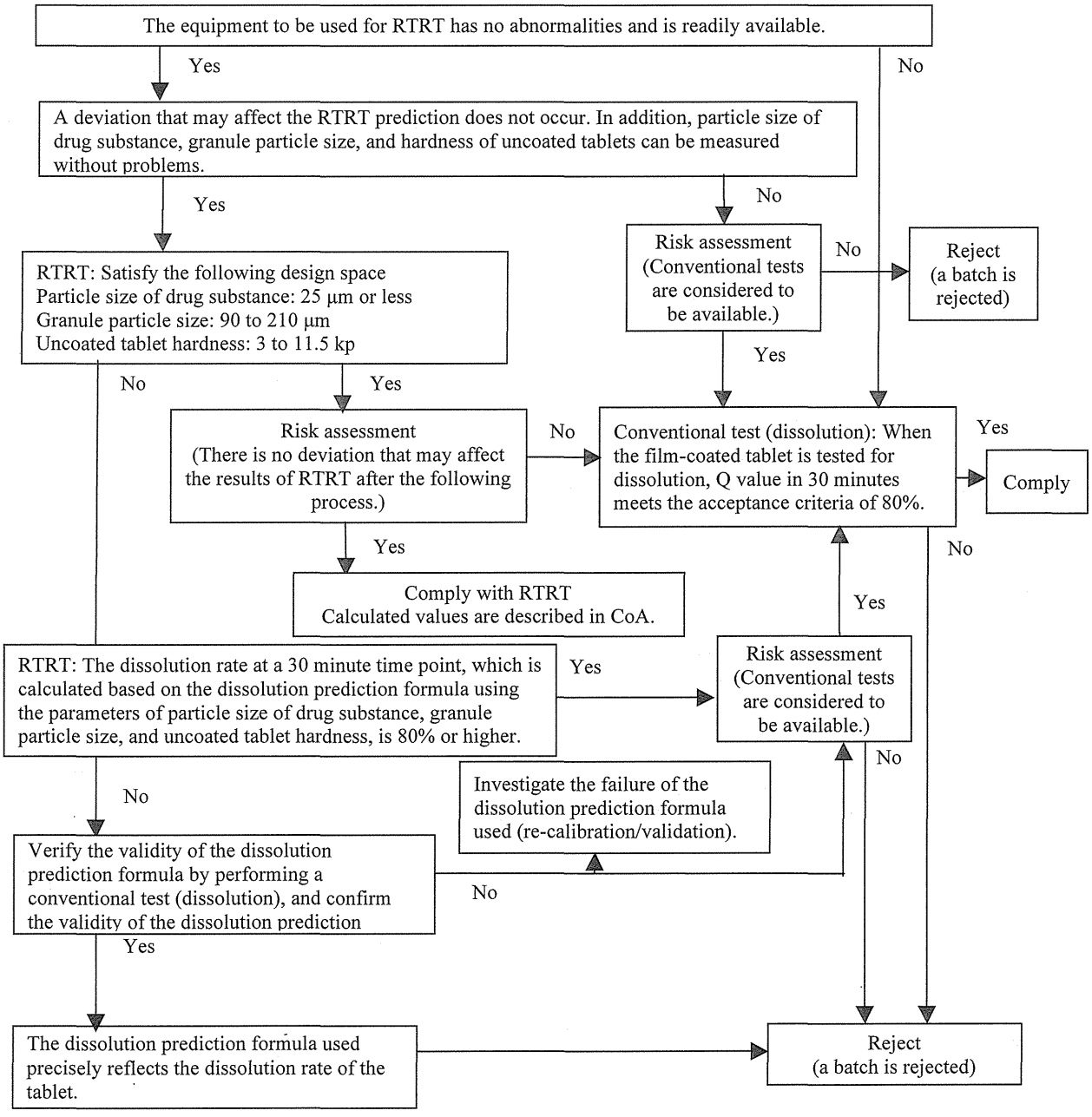
2.3.P.5.2.4.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.4

2.3.P.5.2.4.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the following decision tree.



2.3.P.5.2.5 Assay

2.3.P.5.2.5.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.5

The content is calculated by averaging each content of 200 tablets, determined with an NIR method in Section 2.3.P.5.2.3.1.

2.3.P.5.2.5.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the decision tree described in 2.3.P.5.2.3 Uniformity of Dosage Units.

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

2.3.P.5.3.1 Validation of Test Methods for RTRT(Analytical Procedures)

The validation was performed for the on-line NIR method to determine drug substance concentrations of uncoated tablets in the tableting process and the at-line NIR method for identification in the inspection process.

2.3.P.5.3.1.1 Drug substance concentrations of uncoated tablets <on-line NIR method>

(1) Preparation of Calibration Model (Calibration)

Tablets containing 5 levels of drug substance (60, 80, 100, 120, and 140% of the labeled amount) were prepared. The drug substance content was determined with spectra from NIR method and a conventional method (HPLC) using 5 tablets at each level, and was incorporated into the calibration model. Instrument B from Company A and Software Y from Company X were used for NIR measurement and the analysis, respectively.

The results of optimization of analytical parameters for the calibration model were as follows. It was confirmed that the loading spectra used in the calibration model were similar to the NIR spectra of the drug substance.

Items	Results
Range of wavelength for the analysis	6100 – 5500 cm^{-1}
Spectrum pre-treatment conditions	First derivative + Vector normalization
PLS component number	3
Multiple correlation coefficient	0.985
Prediction error	0.67%

(2) Test of the Calibration Model (Validation)

The drug substance content was determined with spectra from NIR method and a conventional method (HPLC) using tablets (5 levels × 3 tablets) different from those used for calibration. The obtained NIR spectra were applied to the calibration model, which was prepared by the results of calibration of the above (1), and the drug substance content was calculated. The results were as follows, and satisfied the requirements of the validation.

Items	Methods and acceptance criteria	Results
Linearity	The multiple correlation coefficient is 0.97 or higher as a result of test using 5 levels × 3 tablets.	Multiple correlation coefficient: 0.981
Accuracy	Differences in the content of tablets at 70, 100, and 130% levels between HPLC method and NIR method are within ±5% for individual values and within ±2% for the average.	70% level Individual values = 5%, 4%, -3%; average = 2% 100% level Individual values = 3%, -4%, -1%; average = -1% 130% level Individual values = 1%, 2%, -3%; average = 0%
Precision	RMSEP (standard error) is 1.5% or less.	RMSEP: 0.75%
Range	A decision is made based on the results of linearity/accuracy/precision.	70% to 130%
Robustness	Assessment is made using samples containing various variable factors (xx, yy, zz, etc.).	Good linearity, accuracy, and precision were obtained.

(3) Test of commercial production facilities

The prepared calibration model was incorporated into the NIR equipment in a commercial production facility, and the content of tablets was determined with an NIR method in a system reflecting commercial production, and then, the content was determined with a HPLC method.

The standard error between the content determined with an NIR method and the content with a HPLC method was 1.0%, showing a good correlation.

2.3.P.5.3.1.2 Identification <at-line NIR method>

(1) Preparation of a discriminating model (calibration)

A discriminating model was prepared by incorporating 5 tablets from each of the 3 batches of the active and placebo tablets of Sakura Bloom Tablets into a library. Instrument B from Company A and Software Y from Company X were used for NIR measurement and the analysis, respectively.

The results of optimization of analytical parameters for the discriminating model were as follows. It was confirmed that the loading spectra used in the calibration model were similar to the NIR spectra of the drug substance.

Items	Results
Range of wavelength for the analysis	10000 – 7500 cm^{-1}, 6500 – 5500 cm^{-1}
Spectrum pre-treatment conditions	Second derivative
PCA component number	2

(2) Test of the Discriminating model (Validation)

NIR spectra were obtained using, active tablets and placebo tablets different from those used for calibration, and 3 other drug products, and then incorporated into the discriminating model. As the result, only the active tablets complied with the requirement, while other tablets did not have conformity.

2.3.P.5.3.2 Validation of test methods necessary for stability studies (analytical procedures)

The validation of the test methods for Sakura Bloom Tablets was assessed based on "Text on Validation of Analytical Procedures" (Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995) and "Text on Validation of Analytical Procedures" (Notification No. 338 of the Evaluation and Licensing Division, PAB dated October 28, 1997).

<Omitted>

2.3.P.5.6 Justification of Specification and Test Methods

2.3.P.5.6.3 Uniformity of dosage units

2.3.P.5.6.3.1 Uniformity of dosage units (RTRT)

Specifications: When 200 uncoated tablets, which were sampled to represent the whole batch during the tableting process, are tested for assay, the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less and that of 75.0% to 125.0% is 1 or less.

<Description of justification was omitted>

2.3.P.5.6.4 Dissolution

2.3.P.5.6.4.1 Dissolution (conventional test)

Specification: Q value in 30 minutes is 80%.

<Description of justification was omitted>

2.3.P.5.6.4.2 Dissolution (RTRT)

Specifications: The dissolution rate calculated by the dissolution model at the time point of 30 minutes is 80% or higher.

When RTRT is employed for dissolution, justification of the specification is described below.

When a predicted dissolution rate is calculated by the dissolution model, basically due to assessment of the mean dissolution rate, a specification of "dissolution rate at the time point of 30 minutes is 80% or higher" is established as the similar specification of "Q value in 30 minutes is 80%" tested by a conventional method. For the variation of dissolution rate, experiments according to a central composite design were performed using parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness, to calculate the dissolution prediction formula. As the result, the variability was within xx% at any experimental time point, thus, it was considered to comply well with the criteria of S2 on a conventional test. Based on the clinical drugs manufactured to date and the stability data of proposed drug product (manufactured at pilot scale), and the investigational results of commercial scale manufacturing, the solubility can be well assured.

2.3.P.5.6.5 Assay

<Omitted>

Attachment to Sakura Bloom Tablet Mock

Justification of Specifications when the Real Time Release Testing is Employed for Uniformity of Dosage Units

By the Health and Labour Sciences Research Group

The uniformity of dosage units (UDU) test harmonized by ICH in the Japanese Pharmacopoeia (JP), United States Pharmacopoeia (USP), and European Pharmacopoeia (Ph. Eur.), employs a two-step sampling system, 10 dosage units at the first step, and 30 dosage units at the second step, which is listed in "6.02 Uniformity of Dosage Units" of the 16th Japanese Pharmacopoeia (JP16) General Test Process and Apparatus. The acceptance value ($AV = |M - \overline{X}| + ks$) is calculated from the mean of individual contents and the standard deviation. The acceptance criteria are based on a combination of a parametric test (the requirements are met if the AV is less than the limit) and a non-parametric test (the requirements are met if no individual content of the dosage unit is outside of the limit). This test method, however, has the drawback that the content of the active ingredient cannot be followed with time due to sampling from the final drug products.

When many samples are treated with PAT (Process Analytical Technology), which is different from a small size of 10 or 30 tablets, it is most reasonable to compare the consumer's risk with the producer's risk to ensure the acceptable quality specified in the pharmacopoeia. These relations are shown as an Operating Characteristic (OC) curve in Figure 1. When establishing the specifications, it is necessary to consider that large sample sizes increase the probability of detecting samples falling outside the range compared with the conventional method. To ultimately ensure the quality of the products released after passing tests, the acceptance rate is less than 5 to 10% that corresponding to the consumer's risk. In other words, it is unlikely that a product will be released with a quality worse than this level. Whereas, in the case of PAT, too much producer's risk will increase the risk of not continuing production.

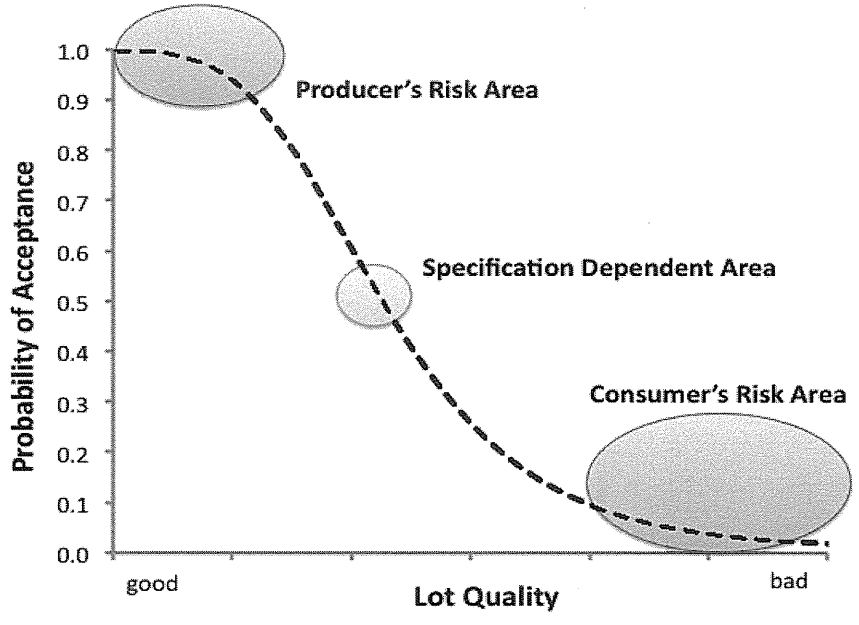


Figure 1. The relationship between consumer's risk and producer's risk in the OC curve.

The research group has established the specifications of Sakura Bloom Tablets, referring to the Large-N method [1][2] and the modified Large-N method (nonparametric test), which were proposed by the PhRMA for the first time. The OC curves based on the Large-N and modified Large-N methods are shown in Figure 2. Compared with the current OC curve of JP16 (dotted line), the curve of the Large-N method coincides with that of JP16 at the consumer's risk level, but the curve of the modified Large-N method appears more fitted to that of JP16 at the producer's risk level. Although it may be interpreted that the test has simply become stricter, it must be important for the level of the producer's risk to coincide with that of JP16, considering the control of

the product after release, which may lead to reduce the risk of non-conformance after marketing.

Table 1 shows the acceptance criteria for UDU (Ph.Eur.2.9.47 [3]) proposed by the Ph. Eur., which is suitable for PAT. The ALTERNATIVE 1 described in the Ph. Eur. is the same as UDU test described in JP16, the combination of a parametric test (use of acceptability constant k) and a non-parametric test (C1 criteria) while ALTERNATIVE 2 is the combination of 2 non-parametric tests with different limits (C1 criteria and C2 criteria). The comparison of OC curves of these two options (Figure 3) did not show much difference in the producer's risk level between ALTERNATIVE 1 (option 1 in Figure 3), ALTERNATIVE 2 (option 2 in Figure 3), and JP16 (ICH UDU in Figure 3). Therefore, after implementation of RTRT, non-compliance to the specifications is unlikely to be observed at the producer's risk level.

The research group had a discussion about Large-N specifications, on the assumption that it is necessary to pay attention to both consumer's risk and producer's risk. In particular, regarding the specifications for RTRT, the producer's risk is important, and an inconvenience could occur in which the risk of non-compliance to specifications increases in terms of release control, unless the conventional specifications and those for RTRT coincide to some extent. Based on these backgrounds, the specifications of "Modified Large-N" of PhRMA or those of the EU are appropriate as the acceptance criteria of Large-N, and the method of Ph. Eur. seems to be better because it can be used for non-normal distribution risk. The comparison between ALTERNATIVE 1 and 2 of the Ph. Eur. resulted in a recommendation of ALTERNATIVE 2, because it can be easily implemented by companies, and a non-parametric test can have high precision with a large sample size. Therefore, ALTERNATIVE 2 of the Ph. Eur. will be employed for the release criteria for the uniformity of dosage units of Sakura Bloom Tablets.

Sakura Bloom Tablet Mock also uses Real Time Release Testing for the content test, and the mean of individual sample contents used for the uniformity of dosage units is adopted for the content of Sakura Bloom Tablets.

Left figure: Large-N method
Right figure: Modified Large-N method

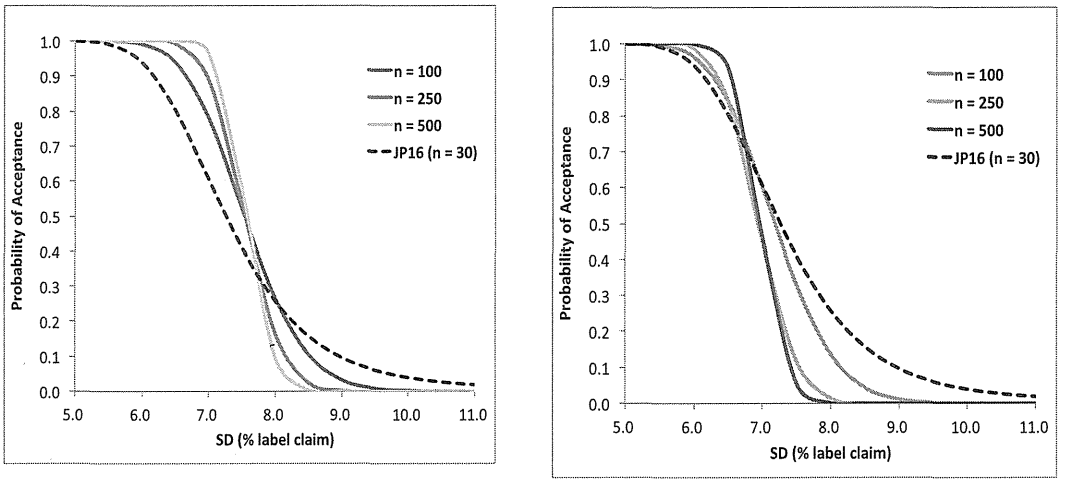


Figure 2. The OC curves of Large-N and Modified Large-N methods.

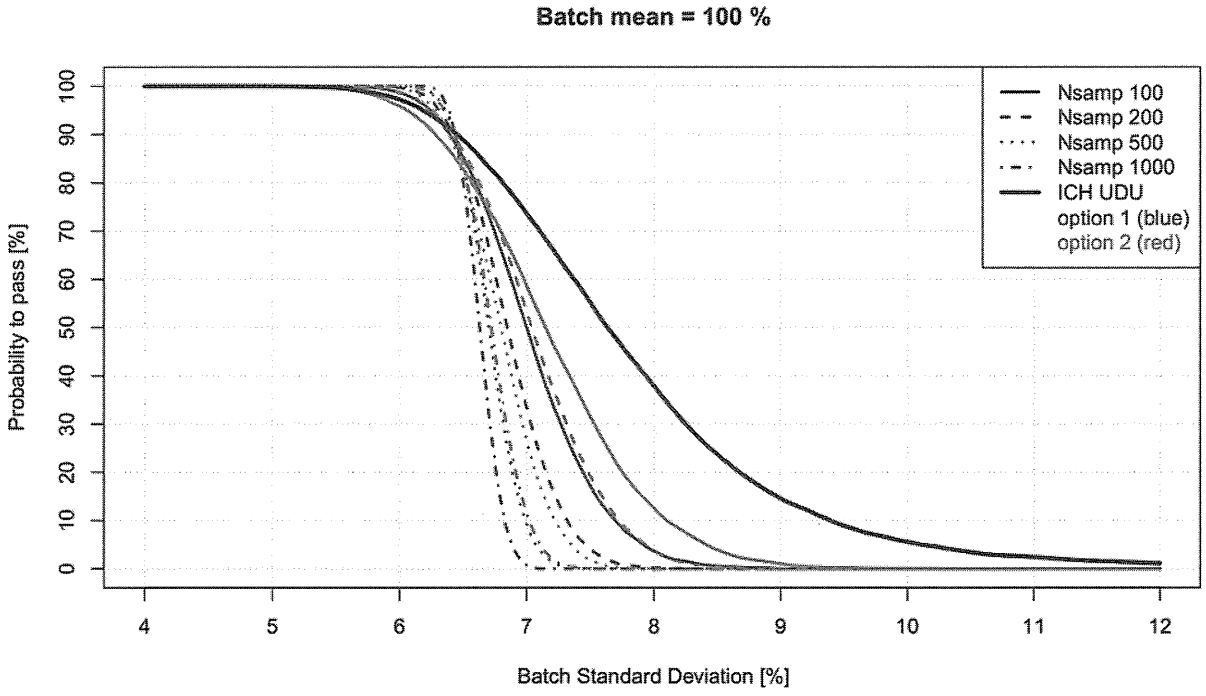


Figure 3. OC curves of selected sample sizes for the adopted 2.9.47 (Alternative 1 and 2, respectively).

Table 1. UDU criteria suitable for PAT, proposed by Ph. Eur..

Sample size (n)	Alternative 1		Alternative 2	
	Acceptance constant (k)	C2 (±25.0%)	C1 (±15.0%)	C2 (±25.0%)
50	-	-	-	-
75	-	-	-	-
100	2.15	0	3	0
150	2.19	0	4	0
200	2.21	1	6	1
300	2.23	2	8	2
500	2.25	4	13	4
1000	2.27	8	25	8
2000	2.29	18	47	18
5000	2.30	47	112	47
10000	2.31	94	217	94

References

[1] Dennis Sandell, Kim Vukovinsky, Myron Diener, Jeff Hofer, James Pazdan, Joep Timmermans, "Development of a Content Uniformity Test Suitable for Large Sample Sizes", Drug Information Journal, Vol. 40, pp.337-344, 2006.

[2] Myron Diener, Greg Larner, Jim Pazdan, Lori Pfahler, Helen Strickland, Kim Erland Vukovinsky, Soren Andersen, "Development of a Content Uniformity Test Suitable for Sample Sizes Beween 30 and 100", Drug Information Journal, Vol. 43, pp.287-298, 2009.

[3] Ø. Holte, M. Horvat, "Uniformity of Dosage Units Using Large Sample Sizes", Pharm. Sci.Technol 36 (10), pp.118-122, 2012

Analytical QbD を適用した分析法開発研究報告書の事例（案）

1. 分析法目標プロファイル（ATP : Analytical Target Profile）

本分析法は、XYZ 製剤中の類縁物質を、ICH Q3B の報告の必要な閾値である 0.1%から規格値 0.2%を含む範囲において定量できる性能を有する。 本分析法は 0.1% から 0.2%の類縁物質を測定するとき、95%の信頼性をもって、測定値が 80%の確率で真値の± 0.02%に含まれる真度及び精度を有している。

上記 ATP の考え方については、別紙にて解説をする。なお、上記で示している数値は事例として示すものであり、これを推奨するものではない。

上記の ATP を満たすため、分析法は以下の性能クライテリア（Performance criteria）を満たすことが要求される。

特異性　製剤添加剤成分の影響を受けず、目的とする不純物を特異的に測定 することができ、十分な識別能を有する。

感　度　定量限界（S/N 比 10 以上）は 0.1%以下であること

範　囲　0.1% から 0.2%を含む範囲において、95%の信頼性をもって、報告値が 80%の確率で真値の ± 0.02%であること。 本範囲において許容される真度及び精度の関係を図 1 に示す。

その他要求事項

直線性　0.05 ~ 1.0% の範囲において直線性を有する。 回帰式 の相関係数は 0.99 以上であり、原点を通過する直線である。

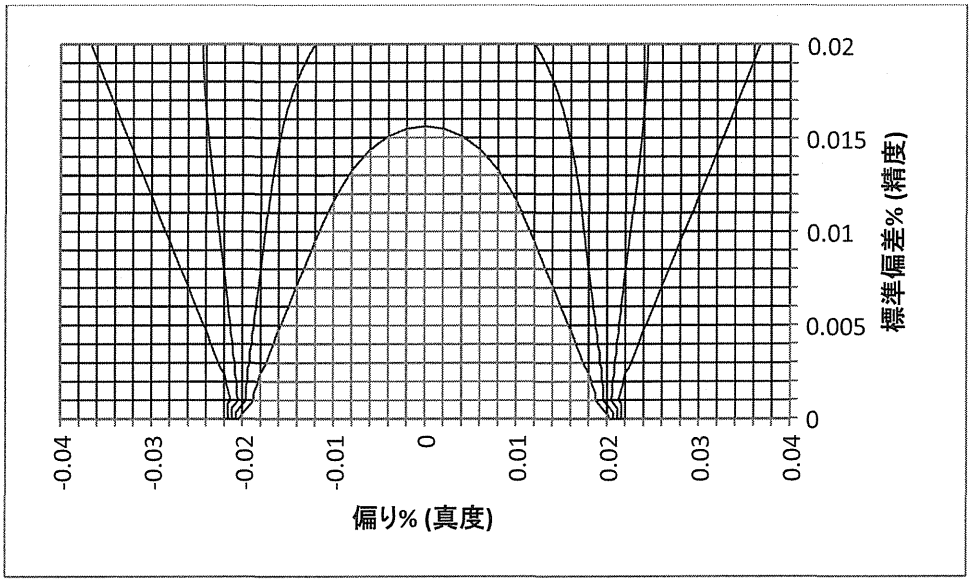


図 1 分析法の真度及び精度の性能クライテリア

分析法の真度（偏り）及び精度（標準偏差）は青色の領域に含まれなければならない

補足説明

その他の要求事項には、分析法の性能クライテリアとしては必須ではないが、分析法の開発するにあたり、開発者が設定する目標を組み入れることも可能である。 今回のケースにおいては、直線性を規定した。一般的に、規定した ATP の要求性能を満たすために分析法が必ずしも直線性を有している必要はなく、多点検量線による定量も可能である中、本試験法では一点検量線法を目標としたことから、直線性をその他要求事項とした。

2. 分析法の開発

2.1 分析手法の選定

本化合物(XYZ)の物理化学的性質、製剤プロセスも考慮した不純物プロファイル、製剤処方情報、及びこれまでに得られている分析手法に関する知識及び経験に基づいて、分析法の性能及び使用性の観点から初期的な評価を行い、候補となる分析手法を選択した。

2.1.1 原薬の物理化学的性質

XYZ の化学構造を Figure X に示す。本化合物の分子量は 300.00、融点は 180°C 付近の不揮発性の有機化合物である。水にはやや溶けにくく、メタノール及びアセトニトリルへの溶解度はそれぞれ 30mg/mL 及び 100mg/mL である。紫外領域に吸収を有し、波長 254 nm に吸収の極大を示す。また、解離基 XXX に由来する pKa は 6.8 である。

本化合物の安定性については、固体状態において熱及び湿度ストレス条件下で安定であることが確認されており、25°C/60%RH、36 箇月及び 40°C/75%RH、6 箇月の保存において品質の変化は認められていない。

2.1.2 製剤の処方

本製剤の製剤処方は、下記に示すとおり、乳糖及びリン酸水素カルシウムを賦形剤とし、湿式造粒法を用いて製造されるフィルムコーティング錠である。

配合目的	規格	成分名	1 錠(103mg)中
有効成分	別記規格	XYZ	30 mg
賦形剤	日局	リン酸水素カルシウム水和物	適量
賦形剤	日局	乳糖	10 mg
崩壊剤	日局	デンプングリコール酸ナトリウム	5 mg
滑沢剤	日局	ステアリン酸マグネシウム	2 mg
ｺｰﾃｨﾝｸﾞ剤	日局	ヒプロメロース	2.4 mg
光沢化剤	日局	マクロゴール6000	0.3 mg
着色剤	日局	酸化チタン	0.3 mg
着色剤	薬添規	三二酸化鉄	微量

2.1.3 不純物の特性(対象不純物)

XYZ の不純物 Imp 1、3、4、6 は原薬に由来する不純物であり、原薬の規格において 0.2%以下に管理されている。これら不純物は、製剤の製造工程中や保存期間中に増加することはなく、Imp 1 は約 0.1%、Imp 3 は約 0.1%、Imp 4 は約 0.2%、Imp 6 は約 0.1%が、恒常的に検出されている。Imp 2 及び 5 に関しては、製剤製造の造粒工程において、XYZ 原薬と添加剤成分である乳糖との反応により生成することが確認されており、Imp 2 は約 0.2%、Imp 5 は約 0.1%が恒常的に認められるが、製剤の保存期間中における増加は認められていない。

2.1.4 分析手法の評価及び決定

分析手法に関する知識及び経験、XYZ の物性、製剤処方及び XYZ の不純物プロファイルに関する情報を基に、候補となる分析手法を選択し、分析性能及び使用性の観点から評価を行った。分析性能としては、特異性、真度及び精度について、使用性としては、入手性、操作性、運用時の費用及び分析に要する時間について評価を実施した。その評価結果は下記に示すとおりであり、分析性能及び使用性の共に高い HPLC-UV 法を、本製剤の分析法として選択し、分析法の開発を行うこととした。

分析性能に関する評価

	Specificity	Accuracy	Precision
HPLC-UV	M	H	H
HPLC-MS	H	H	M
UHPLC-UV	M	H	H
HPLC-MS	H	H	M
CE	M	H	M
TLC	L	M	L

H: 高い性能, M: 十分な性能, L: 十分とはいえない性能

使用性に関する評価

	Availability	Operability	Cost	Time
HPLC-UV	A	A	A	B
HPLC-MS	C	B	B	B
UHPLC-UV	C	B	B	A
UHPLC-MS	C	B	C	A
CE	C	B	B	B
TLC	A	A	A	A

A: 非常によい, B: 満足できる, C: 満足できない

2.2 分析法の設計

2.2.1 分析法の初期スクリーニング

HPLC 分析において、ピーク保持及び分離に大きく影響を及ぼすことが知られているパラメータである、移動相組成(有機溶媒比率)、移動相の pH 及びカラム温度について、スクリーニング検討を行った。 検出波長については、すでに得られているXYZ原薬のUVスペクトル及び目的とする各不純物のUVスペクトルのデータより、220 nmを選択した。 また、分析カラムとしては、AAA、BBB、CCCを用いて検討した。

3 因子 2 水準の一部実施要因計画を用いて実験を行い、ピーク数と最小の分離度に対する重回帰モデルを求めた。 分析カラムについては、最も良好なピーク形状を示した AAA を選択した。カラム温度 30、35 及び 40°C における等高線図を図 2 示す。等高線図で赤色の領域は、ピーク数が 7 未満で目的とする全ての不純物 Imp 1 ~ 6 が互いに、あるいはその他の不純物と分離されていない領域を示し, 青色の領域は、最も近接するピークの分離が分離度 1.5 未満である領域を示している。回帰モデルから、移動相のアセトニトリルの混合比率が 40%付近、pH が 8 付近、カラム温度は 40°C 付近において、ピーク数が 7 以上、最も近接するピークの分離度が 1.5 以上になることが予測された(赤丸で示した中の白色の領域)。

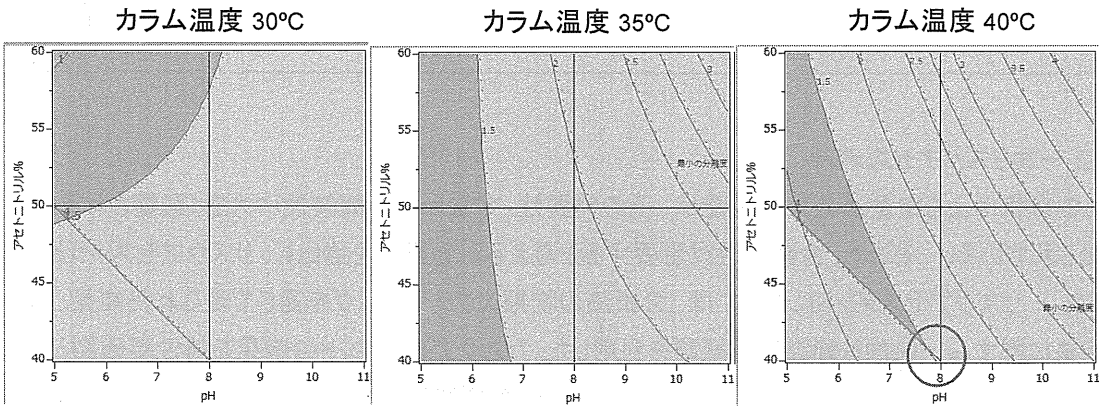


図 2 異なるカラム温度における等高線図 (カラム AAA)

以上の検討結果より、下記の HPLC 条件を候補条件とし、最適化を行うこととした。

HPLC 操作条件

検出器:紫外吸光光度計(測定波長:220 nm)

カラム:AAA (4.6 mmID × 150 mm, 粒子径 5 μm)

移動相:pH 8.0 のホウ酸塩緩衝液 / アセトニトリル混液(60 : 40)

流速:XYZ の保持時間が約 15 分になるように調整する。