Rheological Analysis and Quantitative Evaluation of Wet Kneaded Wax Matrix

Hidaka ABE,*a Tetsuya SUZUKI,a Ayako OOTSUKI,a Kazuhiko OZAKI,a Hirofumi SAMEMOTO,a and Satoru WATANO,b

*a Pharmaceutical R&D Group, Mitsubishi Pharma Corporation; 14 Sunayama, Hasaki-machi, Kashima, Ibaraki 314–0255, Japan; and b Department of Chemical Engineering, Osaka Prefecture University; 1–1 Gakuen-cho, Sakai, Osaka 599–8531, Japan. Received October 9, 2003; accepted February 24, 2004

The properties of the wet kneaded wax matrix were evaluated using a compression tester, whereby a newly proposed $\sigma$ index for the plastic deformation was assessed in the pressure transmission diagram. The $\sigma$ index was indicative of a characteristic of the plastic yield point in the rheological behavior, and presented an initial and abrupt deformation of wet kneaded mass when the wet kneaded mass was subjected to the pressure. The value of $\sigma$ index was confirmed to decrease along with an increase in the plasticity of wet kneaded mass. The wet mass of wax matrix was prepared under various kneading time, and then extruded. The properties of the extruded granules such as pore volume, strength and dissolution were investigated. As a result, it was found that the $\sigma$ index decreased with an increase in kneading time. The granules with small value of $\sigma$ index showed few porosities, large strength and slow dissolution. It was demonstrated that the $\sigma$ index linked the characteristics of wet kneaded mass to the dissolution and the other granule properties. Existence of this link was revealed by $\sigma$ index evaluation relevant to the plasticity. The $\sigma$ index could be a decisive criterion to permit an in-process evaluation of the kneading progress quantitatively, and also useful for anticipating the dissolution of the final granules roughly.

Key words wet kneaded mass; wet granulation; plastic deformation; rheological property; wax matrix; high-shear mixer

Clarification of various factors affecting the quality characteristics of product and establishment of an acceptable range of characteristics play an essential role in stable manufacturing of the sophisticated and desired products. Wet mass properties during agitating granulation process provide strong influence on the quality of final products, and this process is widely used in the pharmaceutical, the plastic and the foods industries. However, agitating granulation process is associated with many operating parameters, which can be classified as apparatus variables (vessel shape and impeller shape), process variables (method of binder addition, wet kneading time and impeller speed) and product variables (powder properties, formulation and binder liquid volume). Both the evaluation of wet granulation and the analysis of observed behavior are very difficult.

Many researchers1–6) have studied the determination method for the critical parameters involved in wet granulation and wet kneaded mass; furthermore, they investigated the effects of such parameters on the granule size, its distribution and density. Although properties of wet granules are not directly and universally quantified by using the torque rheometry and power consumption measurements specific to respective machines, some attempts7–9) have been carried out on the evaluation of granulation and its end point determination. Nevertheless, few reports have focused on the related properties of the wet kneaded mass to the dissolution of sustained-release drug despite of the fact that many different types of sustained-release dosage forms are urgently needed by medical circles to improve clinical efficacies and relevant patient compliance.10)

Watano et al.11–13) have recently demonstrated that properties of the wet kneaded mass are directly characterized by internal pressure transmissions which are determined by using a newly developed compression tester instead of the torque rheometry. Furthermore, it was also documented that the pressure transmissions were strongly associated with water dispersion among the wet kneaded mass. Despite of these available findings, however, the pressure transmissions of the wet kneaded mass are not well identified. What’s worse, to make full use of the features of the wet kneaded mass for manufacturing the sustained-release dosage forms, e.g. wax matrix products, all we have to do is to address the relationship between the pressure transmissions and the drug dissolution. In the present study, the author managed to expand the pressure transmission to the form of the rheological behavior to identify the character of the transmission. Scrutinized investigations about the expanded pressure transmission disclosed the plastic property of the wet kneaded mass that turned out to be the most decisive and direct criterion in the kneading process control. It is because the kneading process subjects the powder sample to be plastic for the preparation of the extrusion granulation. From a theoretical point of view, the evaluation of plasticity from the rheological behavior is suitable for the control of the kneading process; however, the plastic property of wet kneaded mass in sustained-release dosage form has never been evaluated so far.

In this paper, properties of the wet kneaded mass for sustained-release product were evaluated from the newly proposed rheological analysis of plasticity by using a compression tester. The objectives of this study are (i) to assess the plasticity based on rheological analysis thereby monitoring the kneading progress and revealing its correlation with the final dissolution; and (ii) to verify that the rheological analysis is a more important criterion than moisture content and is indispensable for controlling the product quality.

Experimental

Powder Sample Formulation of wax matrix is shown in Table 1. The following ingredients were used: $d$-manitol (Manitol Kao, Kao Corporation., Japan), hydrogenated castor oil (Lovelywax 101, Kawaken Finechemicals
Co., Ltd., Japan) as a matrix substance, crystalline cellulose (Avicel PH-101, Asahi Kasei Co., Ltd., Japan), hydroxypropyl cellulose (HPC-L, Nippon Soda Co., Ltd., Japan) and PMT-1053 (Mitsubishi Pharma Corporation, Japan) as a basic substance of slightly soluble-drug (median size of 25 μm was used). β-Manitol was used instead of PMT-1053 drug in part of experiment. Purified water was used as a binder liquid.

Sample Preparation The wax matrix granules were prepared by kneading and extrusion granulation. After being mixed and kneaded in a high-shear mixer (FS-GS-253, Fukae Powtec Co., Ltd., Japan), the powder samples were granulated with an extrusion granulator (HG-200, Hata Iron Works Co., Ltd., Japan), followed by wet mill processing (Marumerizer Q-230, Fuji Paudal Co., Ltd., Japan).

Evaluation Method During the kneading process, the wet kneaded mass in the high-shear mixer was sampled out from 12 different points to measure both the moisture contents by a Karl Fisher method (Vaporizer CA-06, Mitsubishi Chemical Corporation, Japan) and the pressure transmission with a compression tester. In the extrusion granulation process during which the wet kneaded mass was extruded through the pore of screen, a pressure on the screen was measured by a pressure sensor.

The ground granules were prepared to measure the pore size distribution, roughness of surface, strength and drug dissolution. The pore size distribution and the roughness of the granule surface were determined by a mercury porosimeter (Auto Pore 9220, Shimadzu Corporation, Japan) and by a microscope (Auto VK-8550, Keyence Corporation, Japan), respectively. The strength of the granule was evaluated by a grading degree based on the following Eq. 1:

\[
S = \frac{M_f}{M_R} \times 100
\]

where \( M_f \) is an amount of the initial granules measuring from 840 to 1400 μm in diameter (20 g), and \( M_R \) is a remaining amount of granules over 840 μm in diameter after the initial granules are ground with alumina balls (ϕ20 mm x 8) in a rotating ball mill pot (ϕ120 mm x H120 mm) at 220 rpm for 3 min. The ground granules for the dissolution test were filled up the capsule. The dissolution tests were performed according to the paddle method stipulated in the relevant provision of the Japanese Pharmacopoeia XIV. The dissolution medium (900 ml of 0.1% HCl solutions) was maintained at 37 ± 0.5 °C, while the rotation speed was set at 100 rpm. Samples (10 ml) were taken out at predetermined intervals for a high-performance liquid chromatography (HPLC) assay, and were filtrated (4562DNS, Dainippon Seiki Co., Ltd., Japan). The volume of the dissolution medium was kept at 900 ml by adding fresh medium with the same temperature. Ten microliters (10 ml) were taken out at predetermined intervals for a high-performance liquid chromatography (HPLC) assay, and were filtrated (4562DNS, Dainippon Seiki Co., Ltd., Japan). The volume of the dissolution medium was kept at 900 ml by adding fresh medium with the same temperature.

Kneading Experiment Kneading experiments in this study were so designed (i) to observe the change of σ index in elapsing kneading time and (ii) to obtain the various indices while the wet kneaded mass maintained the same moisture contents.

(i) Quantitative Evaluation of Kneading Progress by the σ Index: After three batches of powder sample were mixed for 5 min, 390 g of purified water was added to each batch for 30 s. The three batches were kneaded for 1, 3 and 5 min, respectively, with main (250 rpm) and chopper (1500 rpm) blades being activated.

(ii) Quantitative Evaluation of Wet Kneaded Mass Including the Same Moisture by the σ Index: After three batches of powder sample were mixed for 5 min, 375 g, 390 g and 405 g of purified water were added to the three batches respectively for 30 s. The three batches of these wet mixtures were kneaded for suitable time until the moisture contents become the same, with main (250 rpm) and chopper (1500 rpm) blades being activated.

Rheological Analysis of σ Index The schematic diagram of the compression tester is shown in Fig. 1. The tester consists of a hydraulic pump, displacement sensor, upper and lower punches, cylinder and personal computer. A cylinder having an outside diameter of 40 mm, an inside diameter of 11.3 mm (cross sectional area was just 1.0 cm²) and a height of 110 mm was placed between the upper and lower punches and the wet kneaded mass of 3.0 g was fed into the cylinder. The upper punch pressed the mass at the moving speed of 5.0 cm/min, and the tester attained a maximum pressure of 1.8 kN. While wet mass in cylinder is pressed, the compression process is assumedly interpreted from a view point of the rheological behavior as follows:

(a) Re-Arrangement (Re): The fed wet mass powder is firstly shifted to the fractional voidage by the upper punch press, and it leads to the re-arrangement.

(b) Plastic Deformation (PD): The re-arranged wet mass powder is immediately deformed to fill the internal voids, and it causes the applied pressure to transmit from the upper to the lower punch. The amount of transmitted pressure from the upper punch press is amplified by the medium of dense deformed mass.

(c) Continuous Behavior (CB): The deformed wet mass powder is completely filled between the upper and lower punches and it is regarded as continuous behavior. It makes the pressurediffused to the inside wall of cylinder. The downward transmission is inhibited by the diffusion of pressure. The fed wet mass in cylinder does not transmit the pressure, until the re-arrangement takes place and completes. And the amount of transmitted pressure is amplified by the upper punch press through the deformed wet mass. Finally, the downward transmission is inhibited by the diffusion of pressure. Within the three mechanical steps of wet kneaded mass in the compaction process, it can appear that the transmission from upper to lower punch increases as the upper punch press increases, and that the ratio of changed transmission is different in each step.

In case of compressing powder bed, pressure of upper punch delivered to the lower punch and the change in the pressure transmissibility can be obtained by the following Eqs. 2 and 3:

\[
G_P = \frac{P_U - P_R}{P_P} \times 100
\]

\[
G_R = \frac{d}{d \log P_C}
\]

where \( G_P \), \( P_U \), \( P_R \) and \( G_R \) denote the pressure transmission, the pressures of lower and upper punch and the pressure transmissibility, respectively. The pressure transmissibility was based on the compaction curve \( G_R \) and the consolidation curve \( \frac{d}{d \log P_C} \) and the logarithm in Eq. 3 was applied to distinguish clearly the three steps of the compaction process according to the change in the rheological behavior. The pressure transmissibility under the applied upper pressure is plotted as the pressure transmission diagram, as shown in Fig. 2. A series of pressure transmissibility data in the diagram was characteristic of a sharp rise and a subsequent steady state, which divided into the three regions in accordance with rheological behavior.

In the pressure transmission diagram the transition between regions Re and PD can correspond to the plastic yield point where shear rate commences the change in response to application of a shear stress. This is because the \( G_R \) begins to change through the pressure absorbed by the com-
pressed wet mass from upper punch press, resulting in that the pressure transmissibility abruptly increases, while the mechanical structure changes; in other words, the wet mass powder is deformed, whereby internal voids are filled. Therefore, the plastic yield point, where the plastic deformation takes place in the wet kneaded mass, presents the degree of plasticity in the wet kneaded mass.

The plasticity in the wet kneaded mass is depended on the quality of being easily deforming and the capability of being moulded into any form. Especially the plasticity is the essential characteristic and the requirement of kneading process, because the kneading process is employed to provide the wet kneaded mass plasticity, which plays an important role in the preparation of the extrusion granulation. The plastic wet kneaded mass is easily extruded through the pore of basket screen that imposed the friction and deformation, resulting in completion of the extruded granules. The extrusion process mainly relied on the degree of plasticity of wet kneaded mass in the kneading process, and then the properties of the extruded granule are highly associated with the degree of plasticity in the wet kneaded mass. As a natural consequence, the plastic yield point in the pressure transmission diagram is really a critical point for the wet kneaded mass in that it decisively affects the physical properties of granules. And also expressing numerically the plastic yield point is required to evaluate the wet kneaded mass quantitatively.

The curve of pressure transmissibility can be fitted by the following Eq. 4, whereby the value relevant to the plastic yield point is obtained:

\[ f(x) = \frac{1}{(\alpha + \sigma \exp(-\beta x)) + \gamma} \]  

(4)

where, \( \alpha, \beta, \gamma \) and \( \sigma \) are the coefficients, and \( \sigma \) is proportional to the plastic yield point. Equation 4, which was based on a sigmoid function, was modified to coincide with experimental data and mechanical changes in rheological behavior. The value of the plastic yield point was converted into the \( \sigma \) index. The coefficient of \( \alpha \) is relevant to the rising and falling of the upper most in the modified sigmoid function, whilst the coefficient of \( \gamma \) is relevant to the rising and falling of the whole modified sigmoid function. The coefficient of \( \beta \) is relevant to the slope in the modified sigmoid function. In the view of rheological behavior in the pressure transmission diagram, the wet kneaded mass achieves better plasticity; in other words, the plastic yield point is more intensely shifted to the left. Such a promising feature is attributable to the fact that the applied pressure immediately generates the sharp rise of pressure transmissibility in the favorable plastic medium. The value of \( \sigma \) index in Eq. 4 is also reduced numerically by the favorable degree of plasticity.

Values for the coefficients of \( \alpha, \beta, \gamma \) and \( \sigma \) were calculated by inserting the typical four data points featuring the sigmoid curve from Re, initial PD, medium PD and CB region into the Eq. 4 and by solving the simultaneous equations of Eq. 4 until all of the data coincided with the calculated approximate equation under the condition of \( r^2 > 0.995 \).

The pressure transmission diagram and modified sigmoid function have been newly designed for assessment of plasticity according to the changes in the rheological mechanism because of the complicated wet mass powder’s characteristics, i.e., non-continuous and continuous with multi phases (gas, solid and liquid). And then \( \sigma \) index was assessed because the plasticity in the wet kneaded mass is the most essential characteristic of kneading process.

**Evaluation of \( \sigma \) Index**  The procedures to determine \( \sigma \) index should be practically suitable for the quantitative evaluation. The suitability was confirmed by evaluating the statistical parameters such as repeatability, robustness and specificity while reproducibility was self-explanatory as shown in Tables 2—5. In this experiment, d-mantol instead of PMT-1053 drug in formulation was used for powder sample. The sample for repeatability was accomplished in one batch, and was measured 3 times. In the robustness, number of sample points was changed, and as to the specification and reproducibility, samples were prepared 3 times under different kneading times. The repeatability shown in Table 2 indicates that the confidence interval of average is narrow, and the accuracy is preferable. As shown in Table 3, the difference between the maximum and minimum is small, and the robustness is preferable. Table 4 shows that the value of \( \sigma \) index becomes smaller with decreasing the time from 5 to 1 min, which clearly verify that kneading time affects the value of \( \sigma \) index. According to the rheological behavior theory,
the numerical smaller value of $\sigma$ index stands for the favorable degree of plasticity of wet kneaded mass. The $p$ value less than 0.05 in Table 5 is considered significant, and $\sigma$ index is regarded to specify the extent of kneading procedure. The confidence interval of standard deviation is narrow, and the scatter of data is small as the reproducibility in Table 5 indicates. All of the items in statistical parameters are satisfactory. It is clear that the $\sigma$ index is suitable for measuring and analyzing the wet kneaded mass. In this connection, the repeatabilities of other coefficients, $\alpha$, $\beta$ and $\gamma$, were also satisfactory, although the repeatability of $\gamma$ which was the worst in the coefficients, was interpreted as the effect of fed sample state in the cylindrical cell.

**Result and Discussion**

**Quantitative Evaluation of Kneading Progress by the $\sigma$ Index** Changes in rheological properties in parallel with progressing of kneading process were evaluated by the proposed $\sigma$ index. After kneaded by high-shear mixer, the wet kneaded mass was extruded to obtain granules, and then the properties of granules were determined.

Figures 3 and 4 show the temporal change of the moisture content, temperature and the $\sigma$ index with the lapse of kneading time. The results illustrated in Fig. 3 indicate that the moisture content decreases and the temperature increases with lapse of the kneading time. Furthermore the standard deviation of moisture content is wider at the kneading time of 1 min, compared to that of 5 min. Both decrease in moisture content and increase in temperature suggest that certain portion of water contained among the wet kneaded mass is evaporated by a heat generated due to the blade rotation with a high shear stress. The decrease in the standard deviations of moisture content means that water is more uniformly dispersed among the wet kneaded mass with the elapsed time of rotating blade accompanied with shear of stress. Watano et al.\textsuperscript{11—13} also reported the improvement of uniform water dispersion during the kneading process, and Evrard et al.\textsuperscript{16} reported the evolution of the product temperature during the melt granulation process in the high-shear mixer. The findings shown in Fig. 4 imply that the value of $\sigma$ index changes in parallel with elapsed time. The small value of $\sigma$ index means that wet kneaded mass undergoes instantly and readily plastic deformation. The wet kneaded mass is thought to be more plastic with lapse of kneading time according to the rheological behavior theory. And then the plasticity is interpreted as the effect of blade rotation with a high shear stress and uniformity of water dispersion in the ingredients.

Figure 5 indicates the pore volume and pore size distributions of extruded granules against $\sigma$ index. The pore volume and mean pore diameter of granules decrease with reducing the $\sigma$ index, which results from longer kneading time. The degree of easy plasticity is related to the pore volume and surface conditions of extruded granules. It is because the wet kneaded mass in the extrusion granulation process is exposed to the friction and the deformation against the wall of screen pores, through which the wet kneaded mass passes. Therefore, the wet kneaded mass attains enough plasticity in accordance with elapsed time, resulting in numerical decrease in the value of $\sigma$ index and pore volume.

Figure 6 reveals the relationship between strength of extruded granules and $\sigma$ index. The strength of granules increases with decrease in the value of $\sigma$ index, which is resulted from a longer kneading time. This result also implies that decrease of $\sigma$ index value is associated with increase in the degree of plasticity. The high strength of granules is thought to be due to the degree of easy plasticity and higher susceptibility to deformation whereby the extruded granules are densified on passing through the narrow pore screen in the extrusion granulation process. Suzuki et al.\textsuperscript{17} reported that the mechanical strength of granules increased with increasing granulation time, while Badawy et al.\textsuperscript{3} also found that the granulation porosity was decreased by either high impeller speed or long wet massing time. The effect of rotation time on physical properties of extruded granules is con-
The granules with a lot of cracks are considered to reduce the strength of granules because of structural characteristic. Figure 7 shows photos of granules with the various $\sigma$ indices observed by Scanning Electron Microscopy (SEM). It is evident that occurrence of crack on granule surface depends on the $\sigma$ index. Easy plastic deformation evolves into generation of smooth and plane granules, leading to reduction of the cracks in number. The plasticity of wet kneaded mass is closely related to the final shape of extruded granules, indicating importance of $\sigma$ index.

Figure 8 indicates the dissolution profiles of wax matrix against $\sigma$ index. The wax matrix with small value of $\sigma$ index, which was obtained by kneading for 5 min, gave prolongation of dissolution. The $\sigma$ index was confirmed to link the drug dissolution. The prolongation of dissolution is generally associated with reduction of pore volume and surface roughness, further evolving into decrease in the surface area of granules. In addition, the prolongation of dissolution is also induced by generation of the firm granules conducive to restraining the disintegration of matrix and maintaining the active ingredient in the matrix. Therefore, the link between $\sigma$ index and the dissolution is attributed to the $\sigma$ index affecting the pore volume and firm granules. The reason is that $\sigma$ index is corresponded to the plastic yield point and indicative of plasticity in the wet kneaded mass.

In the evaluation of kneading process, the surface of extruded granules accomplishes the smooth and firmness in accordance with lapse of kneading time. This is responsible for the findings that plasticity of wet kneaded mass is raised by the kneading time. The plasticity of wet kneaded mass is interpreted as the effect of blade rotation with a high shear stress and uniformity of water dispersion in the ingredients. It is verified that the $\sigma$ index provides a clue to evaluate the plasticity of wet kneaded mass during the kneading progress. The numerical value of $\sigma$ index is decreased by improvement of plasticity. Therefore, the $\sigma$ index links the characteristics of wet kneaded mass to the final granule properties and further, the drug dissolution, indicating that the $\sigma$ index plays a decisive role in evaluating the kneading progress quantitatively, besides being useful in anticipating the dissolution roughly.

**Quantitative Evaluation of Wet Kneaded Mass with the Same Moisture Content by the $\sigma$ Index**

In the kneading and extrusion granulation method, powder samples and water (binder) are kneaded to achieve the plasticity, and then are

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**Figures**

**Fig. 6.** Influence of $\sigma$ Indices Obtained by Various Kneading Times on Granule Strength

Each point represents mean±S.D. (n=3), * $p<0.05$.

**Fig. 7.** Scanning Electron Micrographs of Granules after Extrusion Granulation

(a) $\sigma$ index 0.14, (b) $\sigma$ index 0.28, (c) $\sigma$ index 0.46.

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**Fig. 8.** Influence of $\sigma$ Indices Obtained by Various Kneading Times on Dissolution Profiles of Wax Matrix

$\sigma$ index 0.46, ○; $\sigma$ index 0.28, ▲; $\sigma$ index 0.14, ■ (1 min, ○; 3 min, ▲; 5 min, ■). Each point represents mean±S.D. (n=3).
extruded. Not only high shear stress and high compaction force but also additional water provides a key role for plasticity in the process. In the former experiment of the current paper, both $\sigma$ index and moisture content were changed during the kneading progress. In the next experiment, the wet kneaded masses with various $\sigma$ indices despite of the same moisture content were prepared to demonstrate that $\sigma$ index was the more important criterion as opposed to the moisture content. Incidentally, the moisture content was adjusted from 11.9 to 12.1% in the wet kneaded mass in this experiment, while $d$-manitol instead of PMT-1053 drug in the formulation was used for powder sample.

Figure 9 shows the relationship between the pressure imposed on the screen and the $\sigma$ index under the same moisture content. The result shows that even though the same moisture content is employed, $\sigma$ index affects the extrusion granulation process, thereby the pressure of screen being reduced with decreasing the $\sigma$ index of wet kneaded mass. From the previous experiment, the numerical value of $\sigma$ index is decreased by improvement of plasticity; accordingly, the decreasing pressure of screen is interpreted as the result that the plasticity reaches a level to permit the wet kneaded mass readily press and easily pass through the pores of the screen.

Figures 10 and 11 indicate as a function of $\sigma$ index the pore volume and the surface roughness of granules, which were extruded from the wet kneaded mass. The small value of $\sigma$ index presumably reduced with the $\sigma$ index decreasing. The results of Figs. 10 and 11 finally show that even though the same moisture content is maintained in all of the wet kneaded mass, the pore volume and surface roughness of granules decrease with the $\sigma$ index decreasing. It is demonstrated that $\sigma$ index affects the characteristics of granule surface irrespective of the moisture content. The wet kneaded mass with small $\sigma$ value generates smooth surface, and this finding is consistent with that in the previous experiment in this paper.

In Figs. 12 and 13, each plot shows sizes and strengths of granules against $\sigma$ index, respectively. The percentages of granules measuring larger than $840 \mu m$ in diameter and the strengths of granule increased with decreasing the $\sigma$ index of wet kneaded mass containing the same moisture content. The adequate plasticity of the kneaded mass contributes to formation of longer shapes of the resultant granules; furthermore,
with employment of the sieve method, the granule size tends to be overestimated. It is because that granules easily pass through the pore of the screen with a little friction against the wall of the basket pore, besides a little friction restraining the break of the long shape. The firm granules are conceivable induced by the plasticity, and this result also agrees with that in the previous experiment in this paper. It is demonstrated that \(\sigma\) index indicative of the plasticity affects both the sizes and the strengths of granules irrespective of the moisture content.

Provided that \(\sigma\) indices of wet kneaded mass are varied albeit the same moisture contents, it is verified that the properties of the final granules depend on the \(\sigma\) index. The plasticity of wet kneaded mass is the primary benchmark to decide the fate of the final granules, even though the same moisture content is attained in the wet kneaded mass. Viewed together, we can reach the conclusion that the \(\sigma\) index is the more important criterion than the moisture content. Therefore, the \(\sigma\) index is indispensable for in-process evaluation of the wet kneaded mass during the course of the kneading process.

**Conclusion**

The degree presenting the plasticity, \(\sigma\) index, has been proposed to quantitatively evaluate the wet kneaded mass of wax matrix using the compression tester. It was demonstrated that the \(\sigma\) index decreased with increasing the plasticity of wet kneaded mass. Furthermore, the \(\sigma\) index allowed us to quantitatively evaluate the wet kneaded mass on rheological behavior, while linking the kneading degree of wet kneaded mass (in-process product) to the dissolution of drug from wax matrix (final product). Therefore, the \(\sigma\) index was found to be a very decisive criterion for evaluation of wet kneaded mass to decide the kneading process parameters and to control the kneading process.

**References**