Stabilization Study on a Wet-Granule Tableting Method for a Compression-Sensitive Benzodiazepine Receptor Agonist

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SX-3228, 6-benzyl-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1*H*)-one, is a newly-synthesized benzodiazepine receptor agonist intended to be developed as a tablet preparation. This compound, however, becomes chemically unstable due to decreased crystallinity when it undergoes mechanical treatments such as grinding and compression. A wet-granule tableting method, where wet granules are compressed before being dried, was therefore investigated as it has the advantage of producing tablets of sufficient hardness at quite low compression pressures. The results of the stability testing showed that the drug substance was chemically considerably more stable in wet-granule compression tablets compared to conventional tablets. Furthermore, the drug substance was found to be relatively chemically stable in wet-granule compression tablets even when high compression pressure was used and the effect of this pressure was small. After investigating the reason for this excellent stability, it became evident that near-isotropic pressure was exerted on the crystals of the drug substance because almost all the empty spaces in the tablets were occupied with water during the wet-granule compression process. Decreases in crystallinity of the drug substance were thus small, making the drug substance chemically stable in the wet-granule compression tablets. We believe that this novel approach could be useful for many other compounds that are destabilized by mechanical treatments.

Key words wet-granule tableting; stabilization; degradation; isotropic pressure; die wall strain

A tablet preparation is often the first choice dosage form for new drug substances because it is so easy to handle. Tablets are, however, usually prepared at high compression pressures ranging from approximately 100 to 200 MPa, and it is well known that drug substances are exposed to various factors such as pressure, friction and heat during compression. Enzymes such as α-amylase and lactic-acid bacteria, for instance, are deactivated by compression pressure.[1,2]

SX-3228, 6-benzyl-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1*H*)-one, (Fig. 1) is a benzodiazepine receptor agonist that was newly synthesized at Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan), and was targeted for use as a hypnotic drug.[3—7] This compound is a non-benzodiazepine derivative with demonstrable selectivity for the benzodiazepine ω_1 receptor subtype.[3—7] Although intended to be developed as a tablet preparation, the drug substance turned out to be chemically unstable after compression. The authors announced in the previous report that this instability was due to decreasing crystallinity caused by compression.[8] The investigation concluded that it would be difficult to produce chemically stable tablets containing this drug substance with a conventional manufacturing process and that tablets should be prepared without mechanical treatments such as compression and grinding.[8]

There are several other papers discussing the relationship between crystallinity and chemical stability of drug substances mechanically-treated by compression and grinding.[9—11] It has been reported that addition of lubricants such as macrogol 6000, stearyl alcohol and sucrose fatty acid ester are effective in stabilizing pressure-sensitive compounds in tablets[12,13]; however, these lubricants often have poor compatibility with drug substances.

One particular tablet manufacturing procedure, where tablets produced at quite low compression pressure are moistened and subsequently dried, has been reported as one of the preparation methods of orally disintegrating tablets.[14] In this report, a wet-granule tableting method, where wet granules were compressed and then dried, was investigated due to its advantage of producing tablets of sufficient hardness at quite low pressure.

The objective of this study was to produce chemically stable tablets containing a pressure-sensitive drug substance using a wet-granule tableting method and to clarify the reason for the stability.

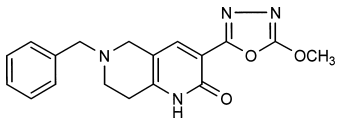

Fig. 1. Chemical Structure of 6-Benzyl-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1*H*)-one (SX-3228, Molecular Formula: $C_{18}H_{17}N_4O_3$, Molecular Weight: 338.37)

Experimental

Materials SX-3228 was synthesized at Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan.

Pharmaceutical excipients: Japanese Pharmacopoeia (fifteenth edition) grade excipients were used. Lactose (Tablettose® 80) (Meggle GmbH, Wasserburg, Germany), cornstarch (Nihon Shokuhin Kako Co., Ltd., Tokyo, Japan), D-mannitol (Mitsubishi Shoji Foodtech Co., Ltd., Tokyo, Japan), low-substituted hydroxypropylcellulose (L-HPC, LH-21) (Shin-Etsu Chemical Industry Co., Ltd., Tokyo, Japan), hydroxypropylcellulose low-viscosity type (HPC L, fine powder type) (Nippon Soda Co., Ltd., Tokyo, Japan), microcrystalline cellulose (MCC, Ceolus® PH-101) (Asahi Kasei Corp., Tokyo, Japan), magnesium stearate (animal origin) (Taihei Chemical Industrial Co., Ltd., Osaka, Japan), light anhydrous silicic acid (LASA, Aerosil® 200) (Nippon Aerosil Co., Ltd., Tokyo, Japan) and macrogol 400 and 4000 (NOF Corp., Tokyo, Japan) were used.

Reagents: Methanol of HPLC grade and all other reagents of analytical grade were purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan.

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Preparation and Storage of SX-3228 Tablets and Granules The conventional tablet consisted of SX-3228 drug substance 5 mg, lactose 55 mg, cornstarch 23 mg, L-HPC 15 mg, magnesium stearate 1 mg and LASA 1 mg (total weight: 100 mg/tablet). The wet-granule compression tablet with a mannitol base formula contained the drug substance 5 mg, D-mannitol 32 mg, L-HPC 10 mg and HPC L 3 mg (total weight: 50 mg/tablet). The wet-granule compression tablet with a MCC base formula contained the drug substance 5 mg, MCC 32 mg, L-HPC 10 mg and HPC L 3 mg (total weight: 50 mg/tablet).

The conventional tablets were prepared by a direct compression method at a pressure of 200 MPa, using a single punch tableting machine (2B, Kikusui Seisakusho Ltd., Kyoto, Japan) fitted with a 6.5 mm diameter punch. Both types of wet-granule compression tablets were produced by compressing wet granules, which were prepared by mixing all the components with appropriate quantities of purified water (20 mg/tablet unless otherwise described) in a mortar. The compression was done at pressures ranging from 20 to 200 MPa, using the same machine fitted with a 6 mm diameter punch, followed by drying at 50 °C for 20 h in a tray drier. Powder paper was slipped between upper and lower punches and wet granules in order to prevent the wet granules from sticking to the punches during the wet-granule tableting and removed from tablets after drying. Continuous tableting was therefore impossible for the wet-granule tableting. The granules used for evaluation were prepared by drying both types of wet granules. For comparison, direct compression tablets were also prepared without water using the same formulas, tableting machine and punch as the wet-granule compression tablets. These tablets and granules were stored in open glass bottles at 80 °C and 60 °C/75% relative humidity (RH) for 14 d in order to evaluate their chemical stability.

Measurement of Tablet Properties Hardness of tablets was determined with a hardness tester (6D, Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland). Disintegration time was measured with a disintegration tester (NT-20HS, Toyama Sangyo Co., Ltd., Osaka, Japan) using 1000 ml of purified water and 30 strokes/min.

Thermal Analysis Thermal behavior was determined using a differential scanning calorimetry (DSC) instrument (DSC2920, TA Instruments, Inc., New castle, DE, U.S.A.). The measurement conditions were as follows: sample weight, about 5 mg; heating rate, 5 °C/min. The thermal analysis was conducted only with the MCC base tablets because of interference by an endothermic peak of D-mannitol at around 160 °C in the mannitol base tablets.

Evaluation of Chemical Stability Chemical stability was evaluated with an HPLC system consisting of an LC-10AS pump, a CTO-10A column oven, an SPD-10A UV–visible detector, an SCL-10AVP system controller, an SIL-10AXL auto injector and a CLASS-VP data system (Shimadzu Corp., Kyoto, Japan). A 150 mm×5 mm internal diameter column packed with octadecyl silica gel of 5 μm particle size, Develosil ODS-5 (Nomura Chemical Co., Ltd., Aichi, Japan) was used at 40 °C. The mobile phase consisted of 65% 0.01 mol/l acetate buffer (pH 4.0) and 35% methanol and the flow rate was set at about 1.0 ml/min. SX-3228 and its degradation products were extracted either from 4 tablets or from an amount of granules equivalent to 4 tablets with 50 ml of purified water–methanol (2 : 3) and 5 μl of the extract was injected. The drug substance and its degradation products were detected at a wavelength of 342 nm and degradation product amounts were expressed as a peak area percentage of the sum of SX-3228 and its degradation products.

Calculation of Porosity Porosity of the mannitol base tablets was calculated from tablet volume and true volume, which was determined from true densities and quantities per tablet component. A true density of purified water was also included in the calculations in order to determine the porosity before drying the wet-granule compression tablets. True densities of components are as follows: SX-3228, 1.50 mg/ml; D-mannitol, 1.48 mg/ml; L-HPC, 1.46 mg/ml; HPC L, 1.22 mg/ml; purified water 1.00 mg/ml. The porosity was calculated according to the following equation:

$$\text{porosity}\ (\%)=(A-B)/A\times 100 \quad (1)$$

where A is tablet volume and B is true volume.

Measurement of Die Wall Strain Die wall strain was measured during tableting using a die with a strain gauge attached to the inside wall. As an indicator of isotropic pressure, the strain amounts of a mixture of macrogol 400 and 4000 (1 : 1) were also measured.

Results and Discussion

Tablet Properties of the Wet-Granule Compression Tablets The relationship between water content during tableting and tablet hardness was examined using the mannitol base wet-granule compression tablets. When the wet granules were compressed at 20 MPa and the weight ratio of water to powder was 0, 20, 30, 40 and 50%, tablet hardness was 1, 19, 34, 46 and 42 N respectively as shown in Table 1. Tablet hardness increased with water content until water content reached 40% whereafter hardness decreased. The optimal water ratio was determined to be 40%, probably because the tablets had excess porosity when water content increased past 40%. The tablets obtained with 40% water content had sufficient hardness and a rapid disintegration property similar to those of the conventional tablets prepared at a compression pressure of 200 MPa (Table 1).

Comparison of Chemical Stability of SX-3228 in the Conventional and Wet-Granule Compression Tablets Table 2 shows chemical stability of SX-3228 in the conventional tablets and the mannitol base wet-granule compression tablets. In the conventional tablets (200 MPa), the total amount of degradation products increased from 0.85 to 5.44 and 11.91% during 14 d storage at 80 °C and 60 °C/75% RH, respectively. By contrast, the wet-granule compression tablets (20 MPa) showed much smaller increases in the total amount of degradation products from 0.77 to 2.49 and 1.95% respectively under the two conditions. The latter tablets thus achieved the desired stability, especially under the high-humidity condition.

Effect of Compression Pressure on Chemical Stability of SX-3228 in the Wet-Granule and Direct Compression Tablets Chemical stability was evaluated for 14 d at 80 °C and 60 °C/75% RH in the mannitol base wet-granule and direct compression tablets prepared at compression pressures

Table 1. Tablet Properties of SX-3228 Conventional and Mannitol Base Wet-Granule Compression Tablets

Sample	Water content (%)	Thickness (mm)	Hardness (N)	Disintegration time[a] (s)
Conventional tablets (compression pressure: 200 MPa)	0	2.8±0.0	46±2	12±1
Mannitol base wet-granule compression tablets (compression pressure: 20 MPa)	0	—[b]	1±1	—
	20	—	19±4	—
	30	—	34±5	—
	40	2.2±0.0	46±4	21±4
	50	—	42±2	—

a) Measuring condition: 1000 ml of purified water, 30 strokes/min. *b*) Measurement was not carried out. The data are expressed as means±standard deviations, $n=3$.

Table 2. Comparison of Chemical Stability of SX-3228 in the Conventional and Mannitol Base Wet-Granule Compression Tablets (Stored in Open Bottles)

Sample	Total amount of degradation products (%)		
	Initial	After 14 d at 80 °C	After 14 d at 60 °C/75% RH
Conventional tablets (compression pressure: 200 MPa)	0.85±0.03	5.44±0.07	11.91±0.39
Mannitol base wet-granule compression tablets (Compression pressure: 20 MPa)	0.77±0.04	2.49±0.01	1.95±0.03

The data are expressed as means±standard deviations, $n=3$.

of 20 and 100 MPa. This evaluation was conducted merely in order to clarify the effect of compression pressure on the two types of tablets, as we have shown above that a pressure of only 20 MPa was sufficient for wet-granule compression tablets with a 40% water content. In contrast, the direct compression tablets were fragile even at 100 MPa. The stability results are summarized in Fig. 2. The initial total amounts of degradation products of all the samples were between 0.74 and 0.82%. In the wet-granule compression tablets, even at 100 MPa, increases in the total amount of degradation products at 80 °C and 60 °C/75% RH were only 1.48 and 0.81% respectively, which is about the same level as seen in the uncompressed granules. In the direct compression tablets, however, the increases in the total amount of degradation products at 80 °C and 60 °C/75% RH were 3.04 and 6.24% respectively at 100 MPa and compression pressure dependence was clearly observed. The results on the MCC base tablets indicated a similar tendency, even though the differences between the two compression methods were small in comparison with the differences seen in the mannitol base tablets (data not shown). The effect of compression pressure on chemical stability was thus smaller in the wet-granule tableting method than in the direct compression method. The mechanism of this stabilization was then investigated.

Thermal Analysis of SX-3228 Drug Substance in the Wet-Granule and Direct Compression Tablets The result of thermal analysis of the intact SX-3228 drug substance in our previous report indicated that the exothermic peak due to the methyl rearrangement reaction shifted toward lower temperature as crystallinity decreased.[8] It was difficult to determine crystallinity of the drug substance in the tablets accurately by powder X-ray diffraction analysis, because the weight ratio of the drug substance in the tablets was only 10%. DSC analysis of the drug substance in the MCC base wet-granule and direct compression tablets was therefore conducted in order to evaluate the extent of damage to the crystals by compression. Table 3 presents the exothermic peak temperature (the degradation temperature) of the drug substance in the MCC base tablets. In the direct compression tablets the degradation temperature decreased from 180.5 to 177.7 and 173.2 °C after compression at pressures of 20 and 100 MPa respectively, and decreased with increasing compression pressure. In contrast, in the wet-granule compression tablets the degradation temperature just slightly decreased from 181.8 to 181.3 and 177.8 °C respectively at the two levels of compression pressure. These results showed that decreases in crystallinity due to compression were considerably smaller in the wet-granule compression tablets compared to the direct compression tablets.

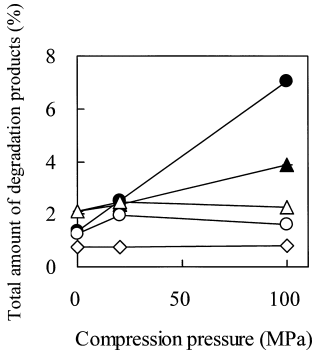

Fig. 2. Effects of Compression Pressure on Chemical Stability of SX-3228 in the Mannitol Base Tablets Prepared by the Different Methods

After 14 d in open bottles at 80 °C and 60 °C/75% RH. ◇, wet-granule compression (initial); △, wet-granule compression (80 °C); ○, wet-granule compression (60 °C/75% RH); ◆, direct compression (initial); ▲, direct compression (80 °C); ●, direct compression (60 °C/75% RH). The data are expressed as means±standard deviations, $n=3$. Symbols ◆ are hidden behind symbols ◇ because their values are almost the same.

Porosity of the Wet-Granule and Direct Compression Tablets Figure 3 shows the relationship between compression pressure and porosity of the mannitol base wet-granule and direct compression tablets. Porosity of the direct compression tablets decreased from 36.8 to 19.2% with increasing compression pressure from 20 to 100 MPa. However, porosity of the wet-granule compression tablets after drying was between 28.6 and 38.5% and did not change considerably when compressed at the same range of pressure. We believe that almost all the empty space in the tablets was occupied with water during the compression process, since at compression pressures between 20 and 100 MPa, the porosity of the wet-granule compression tablets before drying (calculated including water) was almost always less than 10%. These results suggested that the reason why the crystallinity of the drug substance did not drastically decrease by compression was because isotropic pressure, as in liquids, was exerted on the drug substance crystals.

Die Wall Strain During the Wet-Granule and Direct Compression Process There is a die compression method and a hydrostatic-pressure method to compress powder and granules, and in the latter method crystal strain is unlikely to arise because isotropic pressure is exerted on the powder and granules.[15] Die wall strain was measured during the wet-granule and direct compression process of the mannitol base tablets in order to examine pressure transmission in tablets. As presented in Fig. 4, the strain during the wet-granule

Table 3. Effect of Preparation Methods on Degradation Temperature of SX-3228 in the MCC Base Tablets

Preparation method of tablets	Degradation temperature (°C)		
	Granules	Tablets (20 MPa)	Tablets (100 MPa)
Wet-granule compression	181.8±0.1	181.3±0.1	177.8±0.2
Direct compression	180.5±0.2	177.7±0.2	173.2±0.1

The data are expressed as means±standard deviations, $n=3$.

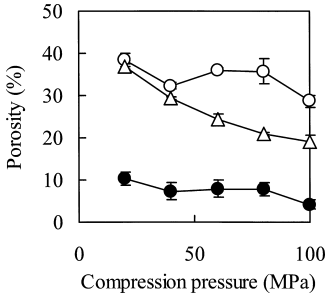

Fig. 3. Relationship between Compression Pressure and Porosity of SX-3228 Mannitol Base Tablets Prepared by the Different Methods

●, wet-granule compression (before drying); ○, wet-granule compression (after drying); △, direct compression. The data are expressed as means±standard deviations, $n=3$.

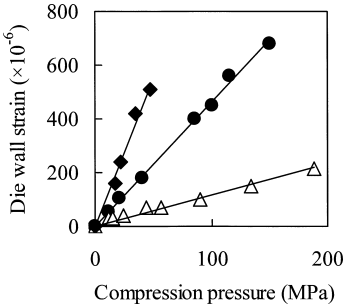

Fig. 4. Relationship between Compression Pressure and Die Wall Strain of SX-3228 Mannitol Base Tablets Prepared by the Different Methods (n=1)

●, wet-granule compression; △, direct compression; ◆, macrogol 4000+400 (1 : 1).

compression was about four times larger than that during the direct compression, although it did not reach the levels of the macrogol mixture, which was the indicator of isotropic pressure. These results demonstrated that near-isotropic pressure was exerted on the drug substance crystals and thus decreases in crystallinity were small during the wet-granule compression process, making the tablets chemically stable.

Conclusion

The SX-3228 drug substance was found to be chemically considerably more stable in wet-granule compression tablets compared to conventional tablets. The reason for this stability was at first thought to be because the tablets could be produced at quite low compression pressure, since the drug substance becomes chemically unstable by mechanical treatments. The drug substance was, however, relatively chemically stable in the wet-granule compression tablets even when high compression pressure was used and the effect of pressure was small. After investigating the reason for this excellent stability, it became evident that near-isotropic pressure was exerted on the drug substance crystals because almost all the empty space in the tablets was occupied with water during the wet-granule compression process. Decreases in crystallinity of the drug substance were thus small, making the drug substance chemically stable in the wet-granule compression tablets. We believe that this novel approach could be useful for many other compounds that are destabilized by mechanical treatments.

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