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COMMUNICATION

Influence of Powder Characteristics of Bulk Substance with Pharmaceutical Processing

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ABSTRACT

The physicochemical properties of crystals can vary with the crystallization procedure employed in their isolation and purification. Moreover, the success of any direct-tableting procedure is directly effected by the quality of the crystals used in this process. We examined the conventional crystallization method employed in the isolation and purification of octotiamine crystals, the active component of the pharmaceutical compound Neuvita®. Our objective was to determine under what crystallization conditions (i.e., supersaturation ratio [pH], temperature, impeller speed) octotiamine crystals with excellent direct-tableting potential could be obtained. Our results indicated that modifications in pH level (from 4.3 to 4.0), i.e., a reduction in the supersaturation ratio, and in impeller speed (from 100 to 78 rpm) are necessary to obtain octotiamine crystals with superior flowability and compressibility compared to the use of the conventional crystallization method.

Thus, with these modifications in the conventional crystallization method, octotiamine crystals can be made that show dissolution rates similar to those of the conventionally made crystals, yet which can be manufactured into tablets using a simpler method (i.e., direct tableting). Also, the tableting powder made from the new crystal type proved to be less adhesive than the conventionally made crystal powder. This property attributed to the new crystal type will allow for more stable automated manufacturing than the conventional crystal type would allow.

INTRODUCTION

The physicochemical properties (i.e., dissolution behavior) and physical properties (i.e., particle size distribution, particle shape, specific volume, repose angle, adhesiveness, compactability, flowability) of products can vary with the crystallization protocol applied to their isolation and purification (1–3). Thus, by varying the crystallization conditions for a given compound, one can vary the design of the resulting crystals (4). We applied this concept in the isolation and purification of octotiamine crystals, the active ingredient in the pharmaceutical compound Neuvita®, which exhibited excellent direct-tableting potential.

Octotiamine is chemically synthesized by reacting the Bunte salt of methyl-6-acetyl-thio-8-chloroocanate with thiol-type vitamin B1 (Fig. 1). Octotiamine crystals are isolated by subsequently treating the above reaction mixture with HCl, adjusting the pH with NaOH, adding octotiamine seed crystals, and again adjusting the pH with NaOH. On first addition of NaOH to the reaction mixture, the formation of emulsion droplets dispersed in the aqueous layer was noted. On further extraction of this aqueous layer with NaOH, octotiamine crystals were obtained.

The isolated octotiamine crystals exhibited physicochemical properties that were measurably superior to those of octotiamine crystals obtained by the conventional crystallization method now employed in the pharmaceutical industry for the isolation and purification of this compound (5). Moreover, because the success of any direct-tableting operation is directly linked to the quality of the crystals used for tableting, it is essential to design pharmaceutical crystals so that tableting is optimized, while dissolution efficiency is concurrently maintained.

In the reaction systems where emulsion was formed, we found that the droplet diameter is directly correlated to the size of the resulting crystals. In such systems, both the solution's supersaturation ratio and the agitation conditions are critical factors in crystal formation. We thus sought to determine the conditions of pH (supersaturation ratio), temperature, and impeller speed under which optimal octotiamine crystals for direct-tableting could be obtained. The results indicated that modifications in pH level (from 4.3 to 4.0), i.e., a reduction in the supersaturation ratio, and in impeller speed (from 100 to 78 rpm) are necessary for obtaining octotiamine crystals with superior flowability compared to that of the conventional crystallization method (Fig. 2).

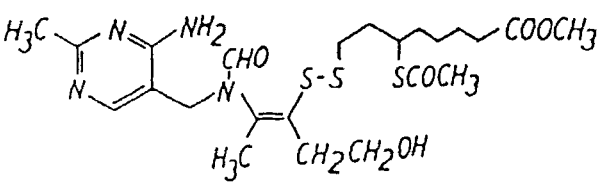

Figure 1. Chemical structure of octotiamine (NV).

MATERIALS AND METHODS

Modified Octotiamine Crystallization Protocol

Octotiamine emulsion extracted with HCl was mixed with 0.5 N NaOH at 28–32°C to adjust the pH to 4.0. Octotiamine seed crystals (1.5%) were then added to this solution. To promote crystallization, this solution was mechanically stirred at 50 rpm for 5 hr at 28–32°C. The impeller speed was then increased to 78 rpm, and 0.5 N NaOH was gradually added to the solution to adjust the final pH to 6.0. After the solution was stirred for 8 hr at 25°C, the crystals were then collected by suction filtration, washed with distilled water, and vaccum-dried to yield a bulk powder of octotiamine.

Evaluation of Octotiamine Crystal and Tableting Powder Characteristics

A comparison was made of the physical characteristics of the octotiamine crystals obtained through the use of our modified method (NV-I) and the conventional method (NV-II). The particle size distribution was determined through the use of JIS sieves and a sieve shaker. The specific volume and repose angle were determined by using a powder tester (Hosokawa Micron Co., Hirakata, Japan). The shape factor, which is the minor-to-major particle diameter ratio, was determined using a phase-contrast microscope (Keyence Co., Osaka, Japan) by randomly measuring 50 crystal particles derived from the application of each crystallization method. The tapping compressibility and adhesiveness of each crystal type was assessed using the parameters a and $1/b$ of Kawakita's method.

Dissolution tests of the NV-I and NV-II crystals were performed by using a rotary basket method (JP XII). The dissolution media used included a simulated gastric fluid (pH 1.2) and an acetic acid/sodium acetate buffer solution (pH 4.0). Dissolution quantity was assessed spectrophotometrically by measuring absorbance at 275 nm.

Blended octotiamine powders (NV-III and NV-IV) were prepared as follows. A 7:3 ratio of 100-mesh-grade lactose (HMS, Tokyo, Japan) and corn starch (Nippon Shokuhinkako Co., Tokyo, Japan) was used as a diluent.

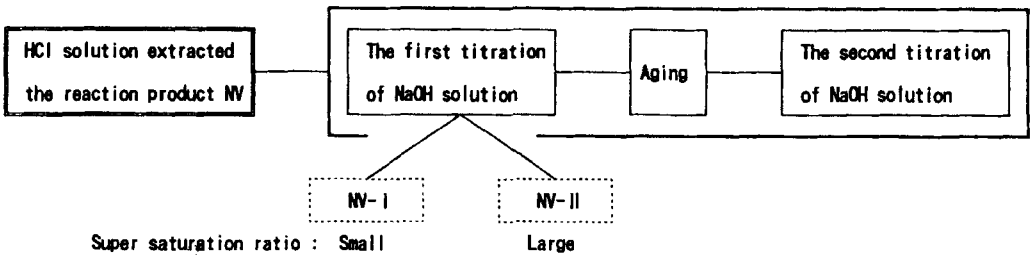

Figure 2. Flowchart of the purifying crystallization process of NV.

This diluent was mixed separately at a 7:3 ratio with the NV-I and NV-II octotiamine crystals and, subsequently, 0.5% magnesium stearate (Taihei Co., Osaka, Japan) was added to the mixtures, resulting in the production of the NV-III and NV-IV tableting powders, respectively. These blended tableting powders were subjected to the same analyses as the NV-I and NV-II crystal powders, except the dissolution tests were not performed.

Evaluation of Tablet Characteristics

The NV-I, NV-II, NV-III, and NV-IV powders were separately compacted into flat-faced 200 mg (8 mm diameter) tablets by using a single-punch press (Okada Seiko, Osaka, Japan). Magnesium stearate was employed as an external lubricant with NV-III and NV-IV. Compressibility of the tableting powders on a continuous tableting process was determined using a rotary press (P-18, Hata, Kyoto, Japan). Tablet hardness (n = 5) was examined by using a tablet-hardness tester (Schreuniger type, Freuind Industrial Co. Ltd., Tokyo, Japan). The tablet tensile strength F (MPa) was calculated by breaking the tablets along their diameter and measuring the load P (kgf), diameter D (cm), and thickness L (cm) at the break point. Tablet diameter and thickness were measured using a micrometer. The following equation was employed in the calculation of tablet tensile strength:

$$F = (0.196 \cdot P)/(\Pi \cdot D \cdot L) \quad (1)$$

RESULTS AND DISCUSSION

Octotiamine Crystal Characteristics

A comparison of the scanning electron micrographs and the sieve profiles of NV-I and NV-II crystals indicated that they differ greatly in shape and diameter (Fig. 3 and Table 1). The majority of NV-I crystals appear as large spherical particles with relatively large intraparticle porosity (Fig. 3 and Table 1). Overall, we found that the particle size distribution of NV-II crystals varied considerably compared to that of the NV-I crystals (Fig. 4 and Table 1).

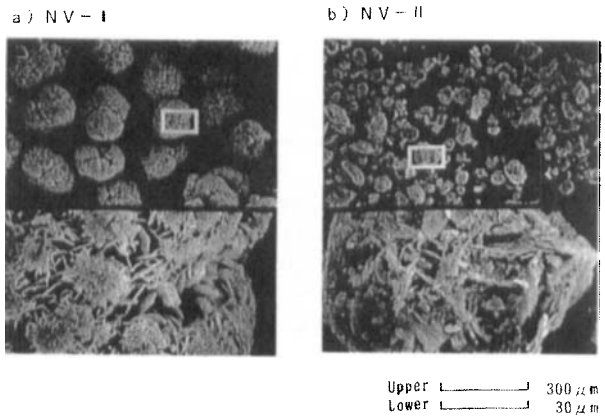

Figure 3. SEM photographs of NV.

The specific volumes and tapping compressibility of the NV-I and NV-II crystals were compared. NV-I proved harder to compress on tapping. This result was probably because of the superior flowability (i.e., lower repose angle) and lower adhesiveness (i.e., lower Kawakita's $1/b$ value) of the NV-I crystals compared to those of the NV-II crystals. Overall, the NV-I crystals have improved material-handling characteristics (i.e., a narrower shape distribution, better flowability, and lower adhesiveness) than those of the NV-II crystals.

Crystal dissolution is a direct indicator of drug bioavailability. No significant differences were noted in the dissolution profiles of NV-I and NV-II crystals (Fig. 5).

Table 1

Powder Properties of the Bulk Powders

Items	NV-I	NV-II
Mass median diameter (μm)	160	80
Geometric standard deviation (σ_g)	1.18	2.96
Specific volume (cm^3/g)		
Loose	3.4	4.1
Tapped	3.0	2.4
Compressibility (%)	12.6	41.5
Repose angle (degree)	34	51
Shape factor	0.86	0.58
Parameters of Kawakita equation		
a	0.12	0.41
$1/b$	6.5	11.0

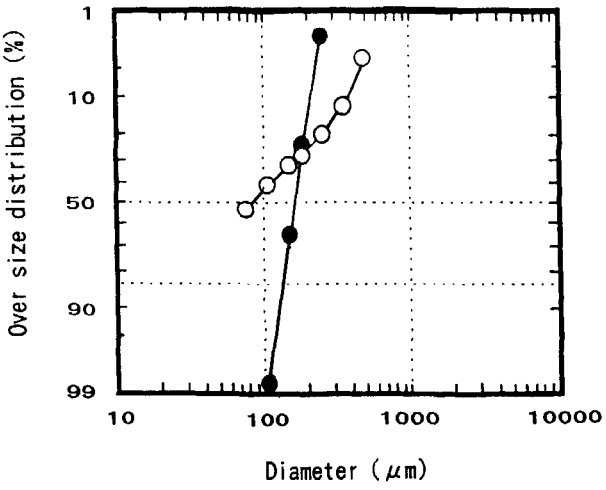

Figure 4. Particle size distribution for the bulk powder of NV. Closed points:NV-I; open points:NV-II.

This observation may be because the NV-I crystals are relatively large spherical crystals with uniform shape and large intrapore diameters; they have nearly the same surface area exposure to dissolution medium as do the NV-II irregularly shaped, smaller crystals.

Evaluation of Direct-Tableting of NV-I and NV-II Powders

To evaluate the compressibility of NV-I and NV-II crystal powders, they were both compacted separately into flat-faced tablets, and their relative thickness and tensile strength were analyzed. The results indicated significant differences in these qualities between the two tablet types (Fig. 6). NV-II could be compressed into tablets with high tablet density at a relatively low applied pressure (39 MPa). The density (i.e., thickness) of NV-II tablets did not change significantly as applied pressure was increased, however, their tensile strength showed a marked decrease at high applied pressure (127 MPa). This observation was probably because of capping, a phenomena marked by internal tablet fracturing. On the other hand, when NV-I was subjected to an increase in applied tableting pressure, tablet tensile strength and tablet density increased as tablet thickness decreased.

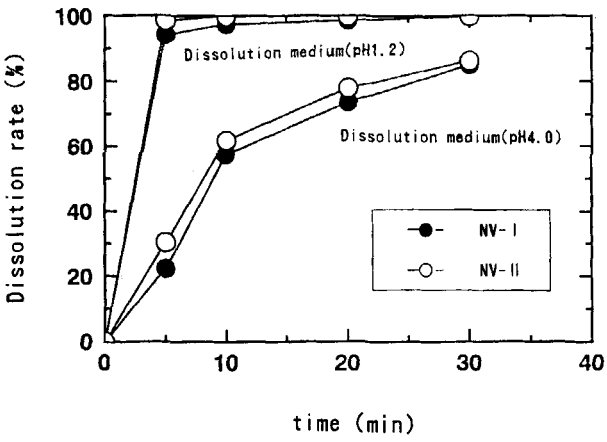

Figure 5. Dissolution profiles of the bulk powders of NV.

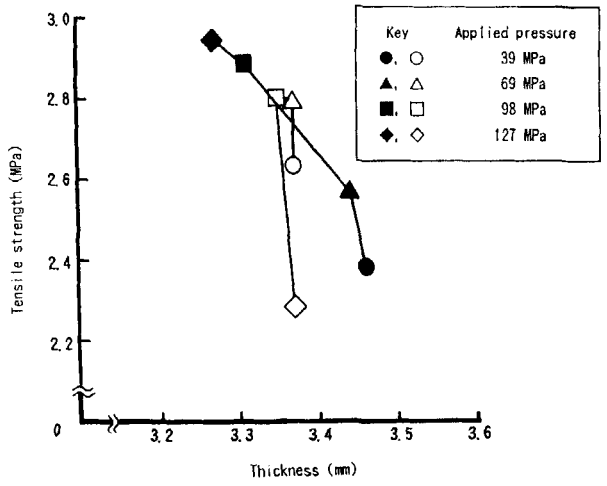

Figure 6. Tensile strength of NV tablets as a function of tablet thickness. Closed points:NV-I; open points:NV-II

Table 2

Powder Properties of the Blended Powders

Items	NV-III	NV-IV
Mass median diameter (μm)	118	92
Specific volume (cm^3/g)		
Loose	2.0	2.3
Tapped	1.4	1.4
Compressibility (%)	28.3	38.4
Repose angle (degree)	43	50
Parameters of Kawakita equation		
a	0.28	0.40
$1/b$	2.35	7.77

Evaluation of Direct-Tableting of NV-III and NV-IV Blended Powders

The blended tableting powders, NV-III and NV-IV, had lower specific volumes than the original crystal powders, NV-I and NV-II, respectively (Table 2). As compared to NV-III, NV-IV had both high repose angle (50°) and Kawakita's $1/b$ value (7.7). The results indicate that NV-IV exhibits both the poor flowability and high adhesiveness of the original NV-II crystals despite addition of diluent. On the other hand, NV-III had both a lower repose angle (43°) and Kawakita's $1/b$ value (2.35). It was hypothesized that the NV-III tableting powder might be suitable for continuous tableting, but no further testing was done.

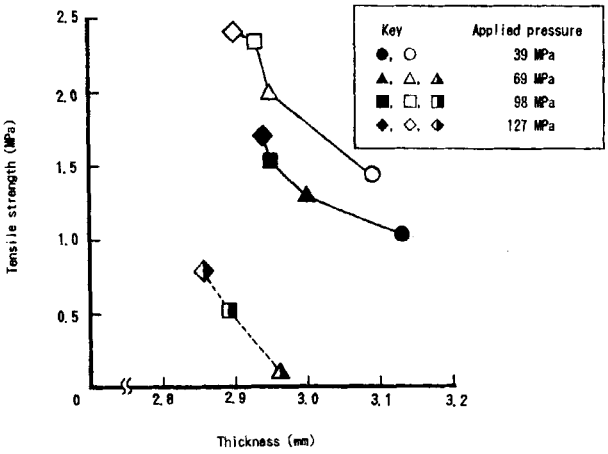

Figure 7. Tensile strength of the direct tableting NV tablets as a function of tablet thickness. Closed points:NV-III; open points:NV-IV; semiclosed points:placebo.

Figure 7 illustrates the relationship between tensile strength on direct tableting of NV-III and NV-IV tableting powders and placebo (diluent alone) as a function of tablet thickness. The tableting powders exhibited higher tensile strength and greater tablet thickness than the placebo. The plot further indicates that NV-IV was more compressible and had a higher tensile strength than NV-III.

Because octotiamine has a low melting point and NV-IV tablets were produced of nonuniform weight in a continuous tableting process, it was hypothesized that NV-II crystals appear at the surface of the NV-IV tablet. On the other hand, in a continuous tableting process, NV-III tablets are produced of relatively uniform weight. This would seem to indicate that NV-I crystals are isolated in the diluent. This would seem to indicate that NV-I crystals are isolated in NV-III tableting powder. That is, in the NV-III tablets, the NV-I crystals are less associated with each other than are NV-II crystals of NV-IV tablets. This isolation of octotiamine crystals, like NV-III tableting powder, reduces the likelihood of punch adhesiveness, friction generation, capping, and tablet melting.

Overall, we suggest that the use of the new crystal type in the manufacturing of octotiamine tablets will allow for a reduction of manufacturing costs, mainly because of the ease with which octotiamine tablets can be produced via direct tableting. Furthermore, throughout this investigation, we found that the new crystallization technique, by which designed crystals with excellent manufacturing properties were obtained, will contribute not only to simplifying and stabilizing pharmaceutical processes (i.e., cost reduction) but also to establishing a general production rational applicable to factory automation.

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