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Direct Agglomeration of Sodium Theophylline Crystals produced by Salting out in Liquid[1)]

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Sodium theophylline monohydrate was precipitated from ethylene diamine solution of theophylline by adding aqueous sodium chloride solution to the system with or without ethanol. The dried precipitates were redispersed in the filtrate without ethanol and were agglomerated with water liberated from the system by adding chloroform and ethanol to the filtrate with agitation. The sedimentation velocity of the agglomerated precipitates and their sedimentation volume at equilibrium were investigated to identify a suitable composition of the medium for agglomeration by gradually increasing the chloroform fraction in the medium. The sedimentation volume slightly increased before dropping drastically at 41% chloroform fraction, at which the precipitates were microagglomerated after passing through a flock stage of high bulk volume. At 56% chloroform fraction, the sedimentation volume sharply decreased again because of secondary agglomeration of the microagglomerates. The sedimentation velocity of the agglomerated precipitates increased with increasing chloroform fraction of the medium in the range above 41%. The agglomerate size increased drastically when the secondary agglomeration occurred. No changes in the sizes and shapes of the elemental crystals were found even after agglomeration. A triangular phase diagram was obtained to described a suitable composition of the medium for agglomeration. It was also proved that simultaneous agglomeration with crystallization was possible in a mixture of four liquids, *i.e.* ethylenediamine solution of theophylline, aqueous solution of sodium chloride, ethanol and chloroform, with a suitable composition.

Keywords——direct agglomeration of crystals; sodium theophylline; crystallization; salting out; spherical agglomeration; simultaneous agglomeration with crystallization

Introduction

The spherical agglomeration technique developed by Capes, Kawashima and others[2-4)] is now accepted as an effective method for the agglomeration of fine particles dispersed in liquid. Kawashima *et al.*[5)] developed a simple and less expensive process to prepare spherical matrixes for prolonged release of drugs with wax-like materials as an alternative to spray-congealing methods[6,7)] by using a modified spherical agglomeration technique.

In the present study, a novel method for agglomeration of fine precipitates prepared by crystallization or salting out was developed by applying the spherical agglomeration technique. Conditions suitable for the agglomeration of sodium theophylline produced by salting out were investigated in liquid. The final goal of this study was to establish a method for direct agglomeration of precipitates or crystals produced in liquid prior to separating them from the system. This agglomeration technique should enable subsequent processes such as separation, filtration, drying, *etc.*, to be carried out efficiently. Furthermore, it is easy to compound the agglomerated crystals obtained with other pharmaceutical powders due to their spherical shape.

Experimental

Crystallization of Sodium Theophylline by Salting out——Ethylenediamine (Nakarai Chemical Ltd., Japan) solutions (13.2 w/v%) of theophylline (Nakarai Chemical Ltd., Japan) were prepared by dissolving 53 g of theophylline in 400 ml of aqueous ethylenediamine solution (5.7 v/v%). Two hundred milliliters

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of sodium chloride solution (15 w/v%) was added to 200 ml of the ethylenediamine solution in a thermally controlled vessel at 37°C with stirring at 400 rpm. After agitation for 60 min, the resultant precipitates were filtered off and dried at 40°C. The dried precipitates and the filtrate were termed A-. Other precipitates, termed B-, were prepared by a modified method. A mixture of the ethylenediamine solution of theophylline (50 ml) and the sodium chloride solution (50 ml) was prepared. After agitation of the above mixture for 5 min, 400 ml of ethanol was added to it and the system was stirred for 60 min at 400 rpm. The resultant precipitates were separated from the system and dried in the same manner as described above.

Identification of the Precipitate Composition——To identify the compositions of the precipitates A and B, sodium theophylline was prepared as a reference compound by evaporating an aqueous mixture of sodium hydroxide (0.2 mol) and theophylline (0.2 mol) at 70°C in a vacuum (20 mmHg). The atomic compositions of the reference compound and precipitates A and B were determined by elementary analysis. The contents of water, sodium and theophylline were determined by the Karl Fisher method (Type MK-S machine, Kyoto Electronics Manufacturing Co. Ltd., Japan), flame photometry (atomic absorption/flame spectrophotometer model AA-610S, Shimadzu Manufacturing Co. Ltd., Japan) at 589 nm and spectrophotometry (Model 100-60 spectrophotometer, Hitachi Manufacturing Co. Ltd., Japan) at 274 nm, respectively. X-ray diffraction patterns of the precipitates were obtained with an X-ray diffractometer (Model JDX, Nihon Denshi Co. Ltd., Japan). The reference compound and the precipitates obtained were confirmed to be sodium theophylline monohydrate, since the elementary analysis values and the contents of water and sodium coincided well with the theoretical values for sodium theophylline monohydrate, as shown in Table I. It was found that the precipitates contained a small amount of sodium chloride together with sodium theophylline monohydrate. Representative analytical data for precipitates A are shown in Table I.

TABLE I. Identification of Precipitates produced by Salting out Sodium Theophylline Monohydrate

	C	H	N	Na[a]	H_2O[b]	Sod. theo.[c]
Reference	38.39	4.13	25.93	12.30	8.17	—
Pre. particle[d]	38.03	4.14	25.83	11.44	8.30	95.48
Theoretical value	38.15	4.08	25.44	10.50	8.17	—

Elementary analysis and contents (%) of water, sodium and sodium theophylline monohydrate

a) Flame photometry.

b) Karl Fisher method.

c) Spectrophotometry.

d) The elementary analysis data of the precipitates were corrected by assuming that the sodium theophylline content was 95.48%.

Agglomeration in Liquid——One gram of precipitate B was dispersed in an adequate amount of filtrate A in a test tube (25 ml, 3.5 cmDx 10 cmh). After adding suitable amounts of chloroform (reagent grade) and ethanol (reagent grade) to the suspension, the system was shaken horizontally at 300 strokes per min for 15 min. The volume of the mixture of filtrate A, chloroform and ethanol was 20 ml. After shaking, the suspension was moved into a measuring cylinder and the settling velocity and sedimentation volume were measured. The sediments were filtered off and dried at 40°C, then the particle sizes of the sediments were measured by sieve analysis. Particle shapes and surface topography of the plain and agglomerated precipitates were investigated by the use of an optical microscope and a scanning electron microscope (Model JMS-SI, Nihon Denshi Co. Ltd., Japan), respectively.

Direct Agglomeration of Precipitates with Salting out——Ethylenediamine solution of theophylline (20 ml) and sodium chloride solution (20 ml) were mixed with agitation at 400 rpm for 5 min. Then 260 ml of ethanol was added to the mixture with stirring and the system was agitated for 30 min, yielding precipitates. By adding 200 ml of chloroform to the system, followed by mixing for 60 min, the precipitates were agglomerated. Simultaneous agglomeration with crystallization was also conducted by mixing the four liquids, *i.e.* ethylenediamine solution of theophylline (20 ml), sodium chloride solution (20 ml), ethanol (260 ml) and chloroform (200 ml). Agitation of the mixture for 90 min yielded agglomerates of the crystals produced by salting out.

Results and Discussion

Sedimentation Velocity and Sedimentation Volume of Agglomerates

The precipitates B dispersed in mixtures with various proportions of the filtrate A (aqueous phase), chloroform and ethanol were shaken, and the sedimentation velocity of the resultant agglomerates was measured in order to find a suitable mixture composition for effective agglomeration. It was found that the sedimentation velocity of the agglomerated precipitates strongly depended on the chloroform fraction in the mixture, *i.e.* the dispersing medium. In the medium without chloroform, the sedimentation volume of the precipitates decreased linearly with residence time. In addition, the sedimentation velocity was slower than that in mixtures containing chloroform. When the chloroform fraction in the medium exceeded a critical value (*e.g.* 41%), the sedimentation velocity began to increase drastically. This was due to the fact that all the precipitates were converted to microagglomerates. The agglomerate size increased with increasing chloroform fraction in the medium, and this resulted in increasing sedimentation velocity, as shown in Fig. 1.

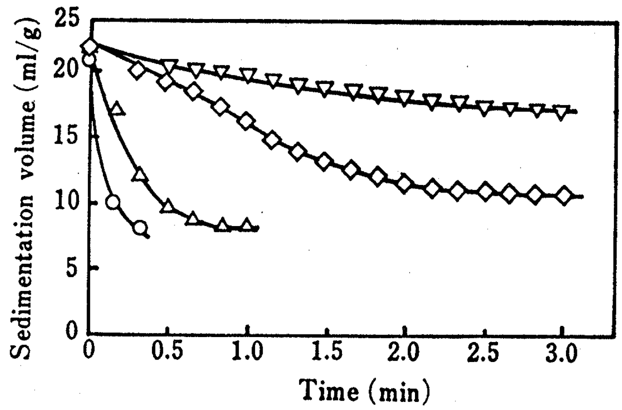


Fig. 1. Sedimentation Velocity of Agglomerated Precipitates

Formulation (aqueous fraction, chloroform fraction, ethanol fraction); ▽, (8, 0, 92) ◇, (8, 42, 50), △, (8, 44, 48) ○, 8, 55.3, 36.7).

Sedimentation volumes at equilibrium are plotted as a function of chloroform fraction in the medium in Fig. 2. As the chloroform fraction in the medium was increased, at first no change in sedimentation volum was found. At a specific fraction point (*i.e.*, 38—39%), the sedimentation volume reached maximum, which suggested that the precipitates became bulky due to aggregation. At this point, it was assumed that the water dissolved in the medium, *i.e.* ethanol and chloroform, was liberated and acted as a collecting liquid for dispersed fine precipitates. Beyond this point, the sedimentation volume dropped sharply, since more liberated water was available for enhancing agglomeration. Above this fraction point, the sedimentation volume increased slightly again. In this region, the system became heterogeneous and bulky again, because of the formation of large agglomerates with irregular

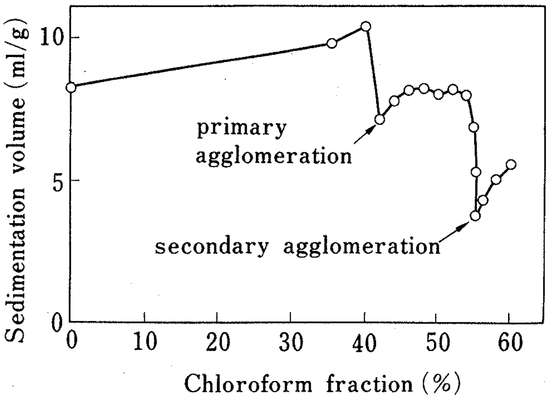


Fig. 2. Sedimentation Volume of Agglomerates as a Function of Chloroform Fraction in a System containing 8% Aqueous Solution

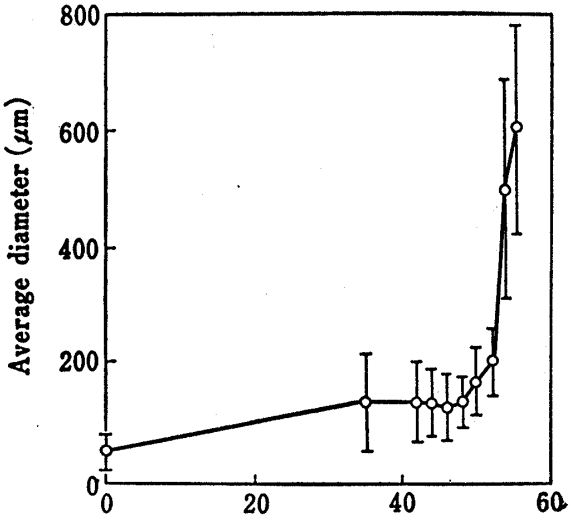


Fig. 3. Average Diameter of Agglomerated Precipitates as a Function of Chloroform Fraction in the System

The size range from 16 to 84% is indicated by bars.

shapes due to coalescence of microagglomerates. Further increase in the chloroform fraction resulted in a second sharp drop of the sedimentation volume due to conversion of the system from a heterogeneous mixture to uniform macroagglomerates. This finding indicates that at this point the amount of collecting liquid was sufficient for macroagglomeration. Further addition of chloroform to the system produced heterogeneous agglomerates again. Finally they formed a paste and the medium was clearly separated into two phases, *i.e.* chloroform phase and aqueous phase in which precipitates were dispersed. The chloroform fraction in the medium imparting the maximum sedimentation volume was assumed to correspond to a critical point for water liberation. The first drop of sedimentation volume and the second drop seen on increasing the chloroform fraction in the medium were termed the primary agglomeration point and the secondary agglomeration point, respectively.

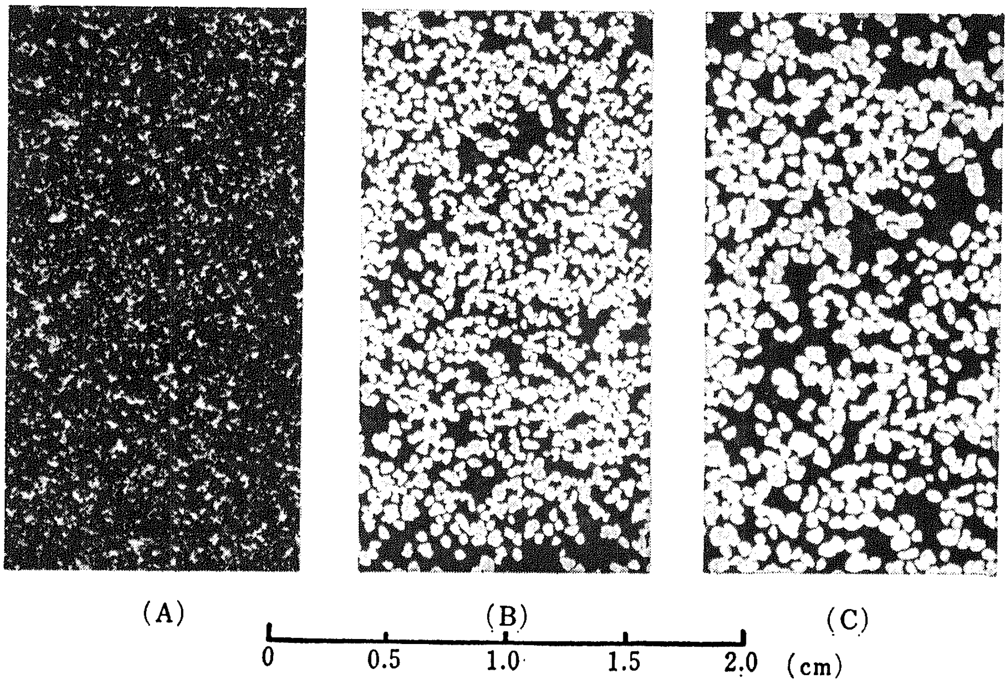


Fig. 4. Photographs of Original Precipitates and Agglomerates

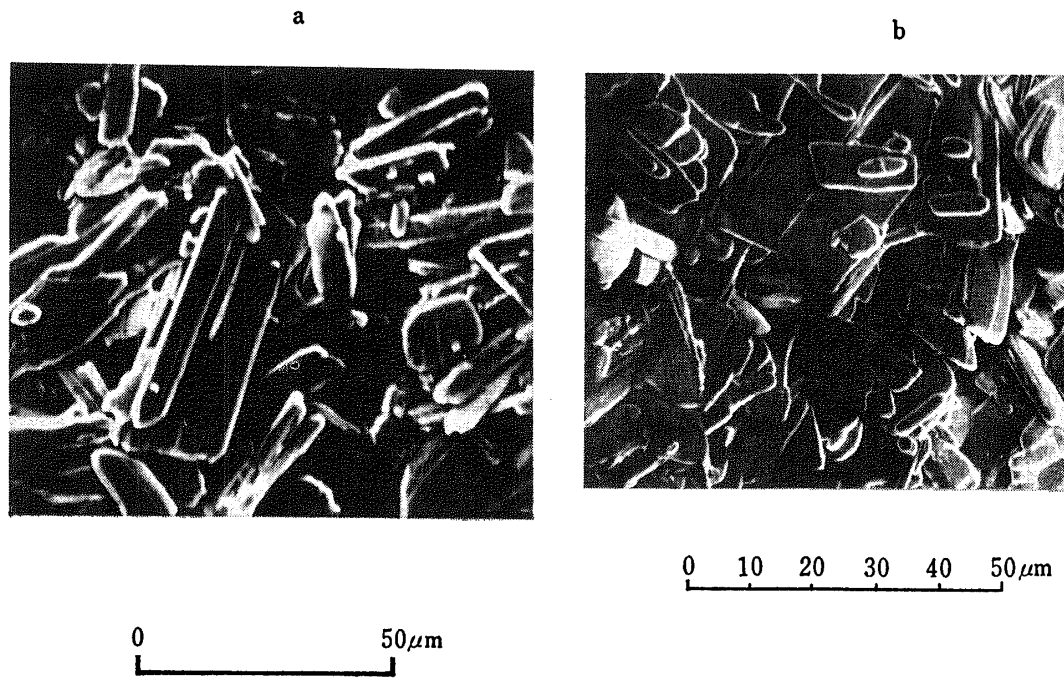
(A), precipitates B. (B) and (C) are agglomerates prepared from the systems (aqueous solution 8%, chloroform 45.3%, ethanol 46.7%) and (aqueous solution 8%, chloroform 55%, ethanol 37%).

Particle Size and Surface Topography of the Agglomerated Precipitates

Average sizes of the agglomerated precipitates are plotted against chloroform fraction of the medium in Fig. 3. At the secondary agglomeration point (chloroform fraction, 56%), the average size of the agglomerates increased drastically as shown in Fig. 3. Particle shapes at the primary and the secondary agglomeration stages are illustrated in Fig. 4. Surface topography of the plain precipitates and the agglomerated ones was investigated by the use of a scanning electron microscope. The original precipitates were rectangular platen crystals with round edges, on the surface of which some minute platen crystals were adsorbed (Fig. 5–a), The crystal sizes varied from 3.3 to 55 μm. The surface of the agglomerates was covered with flat platen crystals, which were closely packed. No changes in the shape and the size of original crystal were found after the crystals were agglomerated as can be seen in Fig. 5-b,c.

Phase Diagram for Agglomeration in Aqueous Solution-Ethanol-Chloroform System

The critical points for the water liberation, and the primary and secondary agglomeration are plotted as a function of the fractions of chloroform and aqueous solution, *i.e.* fil-



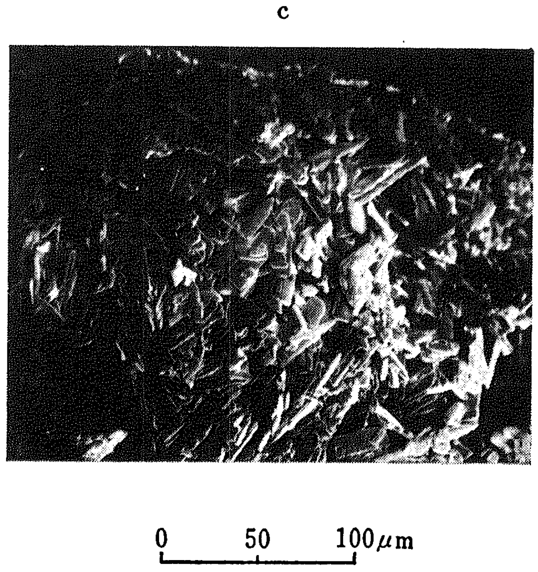


Fig. 5. Scanning Electron Microscope Photographs of Original Crystals B and Their Agglomerates

a, original crystals B. b and c are surfaces of agglomerated crystals B.

trate A, in Fig. 6. When the aqueous solution fraction increased, the range between the secondary agglomeration and the water liberation point decreased sharply. This indicated that the compatible range for agglomeration in the aqua–ethanol–chloroform system decreased with increasing aqueous fraction.

The region capable of agglomeration is illustrated by a shaded region in the triangular phase diagram in Fig. 7. In the region below the critical curve for phase separation, the three liquids were miscible and particles were only dispersed without agglomeration. In the region above the critical curve for secondary agglomeration, the resultant agglomerates formed a paste. In the upper region far from the critical curve of the secondary agglomeration, the system was completely separated into two phases, *i.e.* aqueous solution and chloroform, and the precipitates were dispersed in the aqueous solution phase.

Simutaneous Agglomeration with Crystallization by Salting out

The finding in the previous paragraph suggested that it might be possible to simultaneously agglomerate crystals produced by salting out when adequate amounts of ethanol and

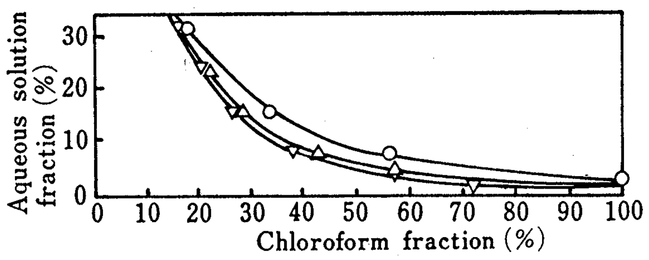


Fig. 6. Two Phase (Aqueous Solution–Chloroform) Diagram for Agglomeration

△, critical curve for primary agglomeration; ○, critical curve for secondary agglomeration; ▽, water liberation curve.

chloroform were added to the crystallization system. This was confirmed by the finding that the crystals were agglomerated directly by adding ethanol and chloroform successively to a mixture of ethylenediamine solution of theophylline and aqueous solution of sodium chloride. This agglomeration was termed successive agglomeration. It was also confirmed that the agglomerates were produced directly from the mixture of the four liquids when a suitable composition was selected as described in the experimental section. This agglomeration was termed simultaneous agglomeration.

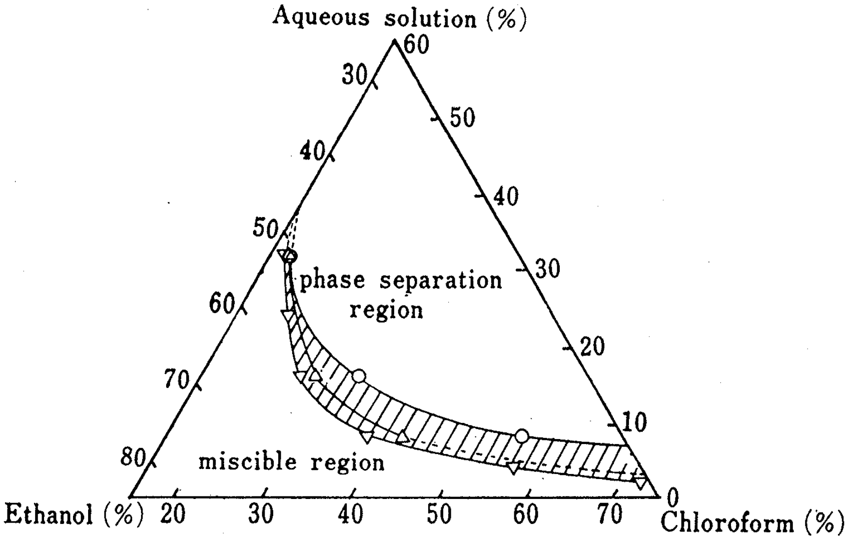


Fig. 7. Triangular Phase Diagram for Agglomeration

△, critical curve for agglomeration; ○, critical curve for secondary agglomeration; ▽, phase separation curve.

The X-ray diffraction patterns of the agglomerates prepared by the successive and simultaneous agglomeration methods and that of the precipitates B are shown in Fig. 8. The diffraction patterns of the precipitates B and both agglomerates coincided well with that of the reference compound, *i.e.* sodium theophylline monohydrate. However, the intensities of the diffraction peaks of both agglomerates were reduced compared to those of the precipitates B and the reference compound. It was found that the contents of sodium theophylline of the agglomerates (63 to 67%) were lower than that of the precipitates B, (92%). The decrease in the content of sodium theophylline might be responsible for the reduction in the intensities of diffraction peaks of sodium theophylline. The diffraction peaks of the agglomerates at 30.9 and 45.8°C for sodium chloride were stronger than those of the precipitates B, suggesting that the contents of sodium chloride in the agglomerates increased. This finding can be interpreted in terms of reduced solubility of sodium chloride in the medium caused by the addition of chloroform to the system.

In conclusion, the present investigation showed that fine particles can be agglomerated immediately when they are produced from an aqueous system by salting out or crystallization by means of adding suitable amounts of ethanol and chloroform to the system. In

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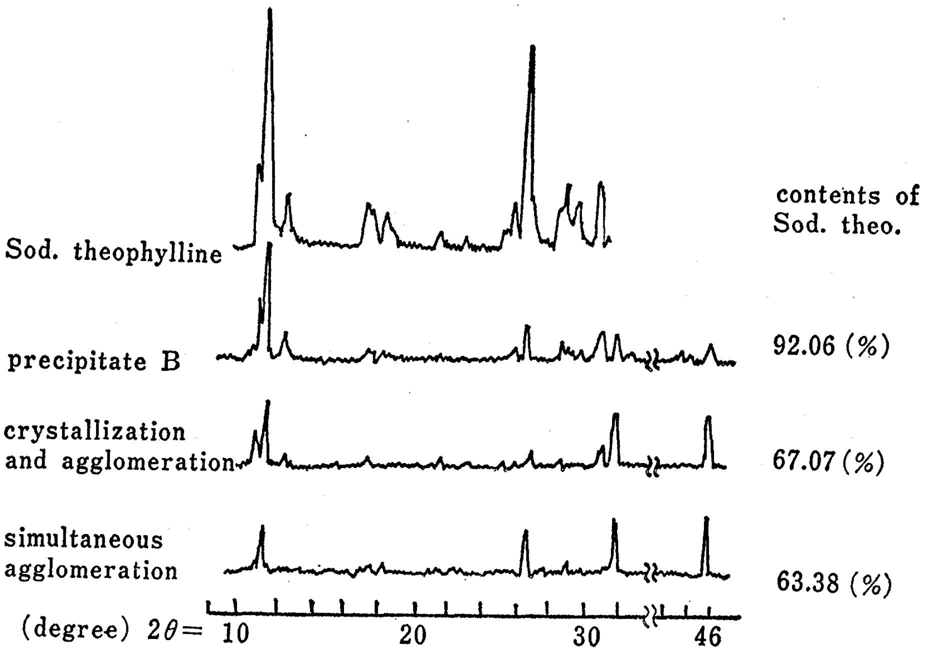

Fig. 8. X-ray Diffraction Patterns and Contents of Sodium Theophylline of Original Precipitates B and Their Agglomerates

the present case, the original shapes and sizes of crystals were unchanged after such agglomeration.

References and Notes

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