The Agglomeration Mechanism of Phenytoin (Antiepileptic) by a Novel Agglomerated Crystallization Technique

Yoshiaki Kawashima, Tetsurou Handa, Hirofumi Takeuchi and Motonari Okumura
Dept. of Pharmaceutical Engineering
Gifu Pharmaceutical University

Abstract

Novel agglomerated crystallization techniques, i.e., neutralization and solvent change, methods, were devised in order to design phenytoin (antiepileptic) crystals so as to be directly compounded during their formulation. The proposed techniques could directly transform the fine precipitated crystals into free-flowing spherical agglomerates during crystallization. Agglomeration by neutralization and solvent change was described in terms of a random-coalescence model and a mixed model with layering, respectively. The micromeritic properties of the agglomerates, e.g. surface topography, particle density and mechanical strength, depended on the agglomeration mechanism. The consolidation of the agglomerates in the neutralization process was represented by a function of the agglomeration rate constants.

1. Introduction

The quality of a powder product and the efficiency with which it is prepared are dependent upon the physical properties of the powder subjected to processing. The primary properties of a powder determine the quality of the product; the secondary properties determine the efficiency with which it is prepared. For example, when a drug that is not easily soluble is prepared, it is desirable to have it done so in a fine crystalline form from the viewpoint of bioavailability. Indeed, the reduction of a powder to finer particles markedly improves its primary properties, such as solubility. On the other hand, it increases the tendency of the particles to cohere so much that their secondary properties, such as flowability and ease of packing, deteriorate. As a result, it becomes necessary to process the powder through a series of additional steps, such as forming a mixture of the ground product with a filler so to become granules. It would be a significant accomplishment if a particle-design method developed whereby powder particles simultaneously assumed both of the desired primary and secondary properties. With a view to developing such a compounded process, these researchers had sought a way to control the secondary properties of crystals by agglomeration, simultaneously controlling the primary properties during crystallization. The primary properties are crystal form, particle size, and the like, while the secondary properties are those of the agglomerates formed from the precipitated crystals. Such a dual control has not been feasible by any of the conventional crystallization methods. The processes dealt with in this paper should extend the crystallization technology.

These researchers previously observed that when a mixed solvent composed of chloroform, ethyl alcohol, and water was used in the crystallization of salicylic acid, a phase separation was forced to occur by adjusting the composition of the solvent and by liberating a slight amount of chloroform in a phase which caused the precipitated crystals to agglomerate into
spherical granules. This phenomenon is due to the capability of the liberated chloroform to function as a bridging liquid\(^2\), which forms a liquid-bridge between hydrophobic salicylic acid crystals. The resultant capillary attraction causes the crystals to agglomerate. In this paper, this theory was expanded to introduce new methods for designing phenytoin in particles, a drug which is not easy to dissolve and the bioavailability of which varies strikingly according to the method used for its preparation. It is known that\(^3\) the concentration of phenytoin in blood, when orally administered, is heavily dependent upon the particle size, and its bioavailability is enhanced by upgrading the fineness of the particles\(^3\). It is desirable, therefore, to develop a new method for designing phenytoin in particles with a view to overall improvement. With this objective in mind, the present research focussed on the development of a new crystallization process by which very fine crystals of phenytoin could be precipitated and directly agglomerated, simultaneously, without the use of any additive, such as a binder. To do this, a neutralization method and a solvent change method were both devised. The agglomerates thereby obtained were subjected to the measurement of their micromeric properties — particle size, density, and mechanical strength (friability) — and the mechanisms of the agglomerated crystallization in the two methods and the process of consolidation of the agglomerates were analyzed.

2. Experiments

2.1 Agglomerated crystallization

Two methods — a neutralization method and a solvent change method — were devised for the agglomerated crystallization.

The neutralization method

Many drugs show either an acidic or a basic property. As an effective method for reducing such a drug to finer particles, there is a neutralizing technique\(^4\) in which the drug is converted into a salt, and then an alkali or acid is added. In the present research, phenytoin (Aleviatin, a product of the Dainippon Pharmaceutical Co.) was dissolved in 1N sodium hydroxide at 40°C, while an aqueous solution of hydrochloric acid in which isopropyl acetate was dispersed as a bridging liquid was prepared and maintained at 20°C in a glass-made cylindrical stirring vessel (diameter 8.4 cm, height 10.8 cm). This solution, which contained isopropyl acetate, was stirred with a 6-vane turbine type stirrer (diameter 4.8 cm, at

![Solubility diagram of isopropyl acetate in agglomerated crystallization system](image-url)
600 rpm) after the addition of the aqueous NaOH solution of phenytoin so as to cause the phenytoin to precipitate in fine crystals by neutralization. Then, depending on the proportion of the isopropyl acetate in the composition, the mixture was observed either to become a homogeneous solution or to separate into an aqueous phase and a phase of isopropyl acetate. Also, it was observed that whereas the crystals which precipitated from the homogeneous solution were dispersed, the crystals which precipitated in the presence of free isopropyl acetate in slight amounts immediately agglomerated by forming a liquid-bridge with the isopropyl acetate. The quantity of isopropyl acetate necessary to cause the agglomerated crystallization was determined by a solubility diagram of isopropyl acetate in a three-component system of common salt, water and isopropyl acetate (Fig. 1 (a)), which was formed separately in consideration of the formation of common salt by neutralization. The agglomerated crystallization was possible in the region along the phase separation curve. The crystals precipitating in a dispersed state were in the left (M) region where the solution formed a homogeneous phase, and the crystals forming agglomerates or slurries were in the right (I) region. Table 1 shows the compositions formulated accordingly. In this research, the agglomerated crystallization was examined both for varied and fixed concentrations of phenytoin, that is, for varied loading quantities of phenytoin against fixed quantities of the liquids used in combination, and for fixed proportions in which the respective quantities of sodium hydroxide and the liberated bridging liquid were adjusted to varied loading quantities of phenytoin. The aqueous hydrochloric acid solution was used in concentrations necessary for the neutralization. Upon the termination of the agglomeration, the pH of the crystallization solvent was examined (pH = 3 ~ 4) so as to confirm that crystallization had been completed. Experiments showed that, in this method, the quantity or concentration of the medicament in the feeding solution could be adjusted relatively easily by changing the concentration of the alkali or acid. Moreover, unlike the solvent change method described next, there was no need to consider whether or not increases in the solubility of the medicament and bridging liquid were attributable to the use of the mixed solvent. Therefore, the conditions for agglomerated crystallization could be set easily by means of the solubility diagram shown in Fig. 1 (a).

### Solvent change method

One commonly known method to reduce crystals to finer particles is to pour a solution of a medicament in a good solvent into a poor solvent4). The present experiments incorporated a process for agglomerating the fine crystals into this known method. Dimethylformamide (DMF) was used as a good solvent, and water was used as a poor solvent. Isopropyl acetate was used as a bridging liquid. In the experiments on the solvent change method based on DMF, agglomeration was examined in two ways: by varying the quantities of bridging liquid against fixed quantities of loading phenytoin, DMF and water; and by varied the quantities of phenytoin against a fixed loading concentration of phenytoin in a DMF solution. A solubility diagram of isopropyl acetate in the mixed solvent (Fig. 1 (b)) was drawn in a manner similar to that in the neutralization method so as to determine the composition in which a crystallization solvent consisting of DMF, water and isopropyl acetate was prepared.

### Table 1 Formulation for agglomerated crystallization

| Method | Phe* [g] | 1N NaOH [mL] | Hydrochloric acid [N, mL] | Isopropyl acetate [mL] |
|--------|----------|---------------|--------------------------|------------------------|
| Neutralization method | 3.0 | 20 | 0.071, 280 | 13.5 |
| | 3.5 | 20 | 0.071, 280 | 13.5 |
| | 4.0 | 20 | 0.071, 280 | 13.5 |
| | 2.0 | 10 | 0.034, 290 | 12.0 |
| | 8.0 | 40 | 0.154, 260 | 16.5 |

| Solvent change method | Phe* [g] | DMF* [mL] | Water [mL] | Isopropyl acetate [mL] |
|----------------------|---------|----------|------------|-----------------------|
| 4.0 | 8 | 292 | 14.5 |
| 4.0 | 8 | 292 | 15.0 |
| 4.0 | 8 | 292 | 15.5 |
| 2.0 | 4 | 296 | 12.8 |
| 8.0 | 16 | 284 | 19.5 |

*Phe* : phenytoin  
*DMF* : dimethylformamide
pared. Table 1 shows the formulated compositions, which are in the shaded region indicating the possibility of agglomeration in Fig. 1. The conditions of the experiments, such as the method of stirring and temperature, were the same as those for the neutralization method.

In order to clarify the agglomeration mechanism of the crystals in the solvent change method, the experiments used a system containing no bridging liquid to compare the results. Crystals were made to precipitate without the addition of a bridging liquid, and then immediately, 5 ml of the suspension of the crystals was sampled and put into a stoppered measuring cylinder (25 ml). To this sample was added an aqueous solution of a surface-active agent [0.1% Tween 80 (polyoxyethylene sorbitan monooleate)] saturated with phenytoin to make 25 ml of the sample. After being stirred by shaking upside down, the sample was left to stand for 30 seconds. Then the top 8 ml portion of the sample was removed, and the same aqueous solution of Tween 80 saturated with phenytoin was added to the remaining sample to make 25 ml of the sample. This same procedure was carried out ten times so as to separate the crystals into dispersed and agglomerated ones. The collected agglomerated crystals were measured with respect to weight and particle diameter under a microscope.

2.2 The micromeritic properties of agglomerated crystals

The agglomerated crystals were evaluated with respect to their micromeritic properties. This was done by measuring the particle diameters of both the agglomerates and the crystals constituting the agglomerates, as well as the apparent density and the friability of the agglomerates.

The particle diameters of the agglomerates were obtained by sieve analysis and those of their constituent crystals by dispersing them in liquid paraffin and using a microscope. The apparent density \( \rho_{ap} \) of the agglomerates was obtained with respect to samples, the weight \( W \) of which was known by first calculating the volume from the diameter \( d \) of the projected area and then by using the equation,

\[
\rho_{ap} = \frac{W}{\sum \frac{\pi}{6} d^3}
\]

The evaluated micromeritic properties included, the friability of the agglomerated crystals because since such agglomerates are assumed to be subjected immediately to drug preparation, pharmaceutical industries attach importance to friability as a mechanical strength. The friability was determined by a procedure in which agglomerates \( (W_o = \text{approx. 3g}) \) correspond to the granule size range \( (297 \sim 1,410 \mu m) \) specified in the Japanese Pharmacopoeia. These were loaded onto a No. 80 sieve (sieve opening 177 \( \mu m \)) and given continuous impacts by a low tap type sieving machine (Model ES-65, product of Iida Manufacturing Co.) to periodically measure the weight \( (W_p) \) of the particles which pass through the sieve. The friability was obtained as \( X = \frac{W_p}{W_o} \).

3. Observations

3.1 The micromeritic properties of agglomerated crystals

The obtained agglomerated crystals were observed to be spherical and to have a free-flowing property. Their particle size was seen to be controlled by the amount of the bridging liquid added to the crystallization system. Figure 2 shows the relationship between the average particle diameter of the agglomerated
crystals and the amount of the bridging liquid used for 30 minutes in a process of agglomerated crystallization. In both methods, an increase in the amount of the bridging liquid used caused the particle diameter of the agglomerates to increase, as already reported\(^5\). As was predicted from the solubility diagrams of the bridging liquid in Fig. 1, the amount of bridging liquid required to yield agglomerates of an equal particle size was more in the solvent change method than in the neutralization method. As shown in Fig. 2, the particle size distributions indicated by a standard deviation had a broad range, and the particle diameters as a whole were larger in the solvent change method than in the neutralization method. The solvent change method presented a solid-liquid interfacial phenomenon which was not observed in the neutralization method because DMF was mixed in the crystallization solvent and bridging liquid.

Figure 3 shows photographs of agglomerates taken by a scanning electron microscope (JSM-T20, product of Nihon Electronics Co.). No difference was observed between the two methods with respect to the shape and particle diameter of the primary crystals that constituted the agglomerates (see Fig. 4), but there were differences in the surface features of the agglomerates and the patterns in which crystals agglomerated. Sub-units of sizes ranging from 40 to 90 \(\mu m\), that probably formed by coalescence, were observed in the agglomerates in the neutralization method, however, the agglomerates in the solvent change method were shown to be favorably spherical in shape. Their surfaces were densely built of plate-shaped crystals, and their structures suggested the agglomeration of crystals by the layering agglomeration mechanism.

**Figure 4** shows the particle size distributions of agglomerates of crystals and crystals constituting the agglomerates, determined by a microscopic method. The particle sizes were.
Fig. 4 Particle size distributions of agglomerates and primary crystals composing agglomerates

larger with respect to the crystals which constituted agglomerates in both methods. The crystals which did not agglomerate in the solvent change method were also larger than the crystals which did not agglomerate in the neutralization method. It is considered that the solubility of phenytoin in the crystallization solvent was enhanced because of the addition of DMF and isopropyl acetate, so that the degree of supersaturation of phenytoin was lowered, and the particle diameter of the precipitated crystals consequently increased\(^6\). In fact the solubility of phenytoin in the crystallization solvent was increased by 1.4 ~ 1.7 times more than the solubility in cases where no bridging liquid was used in the neutralization method. As is clear from Figs. 3 and 4, there was no difference between the neutralization method and the solvent change method with respect to the size of the crystals that constituted the agglomerates; nor was there any difference in the shape or the crystals between the two methods.

Although there were differences in particle diameters and surface features of the agglomerates depending on the method of crystallization described above, the experiments produced spherical agglomerates which were free-flowing, each having a diameter of 0.2 ~ 1 mm and composed of fine crystals with a diameter in the range of 3 ~ 11 \(\mu\)m. It was also observed that the particle diameter of the agglomerates could be changed as desired by adjusting the amount of the bridging liquid used.

Next, the friability of the agglomerates was examined. As shown in Fig. 3, it was observed that whereas the surface of an agglomerate obtained by the neutralization method was jagged and thinly composed of crystals, the surface of an agglomerate by the solvent change method was densely composed of crystals. This structural difference was considered to have a bearing upon the mechanical strength of the agglomerate. The friability of the agglomerates was examined by a test in which they were impacted with a low tap, type sieving machine. The results are shown in Fig. 5. These data were processed\(^7\) by the equation,

\[
R_n(x) = R_0(x) \cdot (1 - Pr)^n
\]

where \(Pr\) represents the probability of breakage per impaction due to abrasion and destruction and is estimated for each number of times \(n\) dropped, and \(R_n(x)\) is the cumulative weight percent over size \(x\) on a sieve with a sieve opening of \(x\) (80 mesh). In the friability test of spherical agglomerates, the relationship between the pulverized fraction \(X\) and the time \(t_f\) is expressed by Eq. (3), which was formulated on the reasoning that the rate of friability is proportional to the surface area of the agglomerates:

\[
\sqrt{1-X} = 1 - \frac{2k\phi}{\rho_\text{ap}D_0} t_f
\]

where \(k\) is the friability rate constant, \(D_0\) is the diameter of the agglomerates prior to the test, \(\rho_\text{ap}\) is the apparent density of the agglomerates, and \(\phi\) is the shape factor. The agglomerates obtained by the neutralization method were pulverized in accordance with Eq. (2) and Eq. (3). As a result, the agglomerates obtained by that method were observed to be progressively pulverized from the surface through abrasion, and the cohesive force (= strength) acting between the constituent crystals was
seen to be uniform. The agglomerates which had been allowed a longer time for agglomeration \( t = \) stirring time) were found to be easier to pulverize, even though they were thought to have become more consolidated. This observation is based on the difference in average particle diameter between the specimens examined \( t = 30 \text{ min}, 586 \mu \text{m}, t = 50 \text{ min}, 741 \mu \text{m} \). In contrast, the agglomerates obtained at \( t = 30 \text{ min} \) by the solvent change method (average particle diameter \( = 776 \mu \text{m} \)), although larger than those obtained by the neutralization method \( (586 \mu \text{m}) \), were hard to pulverize and satisfied neither of the equations. Since they were pulverized as easily as those obtained by the neutralization method in the initial stage \( (< 15 \text{ min}) \) of the test and became hard to pulverize later, a hard nucleus was considered to exist in the interior of the agglomerate obtained by the solvent change method.

From these results it was determined that the mechanical strength of the agglomerates is dependent on the mechanism which is active in the agglomerated crystallization.

### 3.2 The process of agglomerated crystallization and the mechanism of agglomeration

Figures 6 (a) and (b) show the relationship between the average particle diameter and the residence time of the agglomerates obtained by the neutralization method. As shown in Fig. 6 (a), the changes in the concentration of phenytoin in the feeding solution had no bearing upon the average particle diameter of the agglomerates extrapolated for the residence time \( t = 0 \). Subsequently, however, differences were observed in the growth rates of the agglomerates. On the other hand, when phenytoin was fed at a constant concentration but in varied quantities, as shown in Fig. 6 (b), the particle diameters of the agglomerates at the initial stage showed increases corresponding to increases in the quantity of phenytoin but the growth rate of the agglomerate did not change.

The data from the neutralization method in Fig. 6 was rearranged in Figs. 7 (a) and (b). The linear relationships were found between the logarithmic particle diameters and the residence time in the two diagrams. They agreed with the coalescence model\(^8\) formulated by P.C. Kapur. These results also agreed with the results of the electron-microscopic observations shown in Fig. 3.

$$\ln l = k_1 t + C_1, \quad \frac{dl}{dt} = k_1 l$$  (4)

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Fig. 5 Friability of agglomerates
where \( l \) represents the average particle diameter of agglomerates, and \( k_1 \) and \( C_1 \) are constants. When phenytoin was fed in varied concentrations [(a) in Figs. 6 and 7], the phenytoin crystals which precipitated decreased in relationship to the decrease in the concentration of phenytoin, but no change was observed in the quantity of the liberated bridging liquid. It is therefore considered that the rate of the agglomeration of crystals, that is, the growth rate, increased because of increases in the quantity of the bridging liquid per unit weight of the crystals, and that, when phenytoin was fed in varied quantities against a fixed concentration [(b) in Figs. 6 and 7], the presence of the bridging liquid in a changeless quantity per unit

Fig. 6 Average diameter of agglomerates as a function of residence time

![Graph](image1)

Phenytoin (g)/1N NaOH [ml]: ● 3/20, □ 3.5/20, ○ 4/20, ● 2/10, ● 8/40

Fig. 7 Average diameter of agglomerates as a function of residence time

![Graph](image2)

Phenytoin (g)/1N NaOH [ml]: ● 3/20, □ 3.5/20, ○ 4/20, ● 2/10, ● 8/40
weight of the crystals caused the crystals to agglomerate at a constant rate.

Figures 8 (a) and (b) show the growth process of the agglomerates in the solvent change method. No difference was observed between this method and the neutralization method with respect to the shape and particle diameter of the crystals constituting the agglomerates (see Fig. 4), but the particle size of the agglomerates produced at the initial stage was more than twice as large as that of a comparable diameter in the neutralization method. As shown in Fig. 8 (a), the increased use of the bridging liquid enhanced the growth rate of the agglomerates of the crystals. When phenytoin was fed at a fixed concentration, the particle diameter of the agglomerates produced at the initial stage increased for 8 g of phenytoin but showed no difference for 2 g and 4 g, respectively, of phenytoin, as shown in Fig. 8 (b). As described in the aforementioned experiments, an increase in the proportion of DMF in the crystallization solvent results in the bridging liquid as well as the phenytoin having increased solubility in the crystallization solvent. Therefore, a slight change in the recipe strikingly affects the rate of the agglomeration and makes it difficult to set the conditions of the experiments on the basis of the solubility diagram in Fig. 1. The agglomerating process in the solvent change method did not agree with Kapur's Eq. (4) or the layering mechanism\(^9\) of the agglomeration expressed by Eq. (5):

\[
\ln l = k_2 \cdot \ln t + C_2
\]

Figure 9 shows the relationship between the residence time and the size distribution of the agglomerates of the crystals. It was observed that the size distributions of the agglomerates obtained by the neutralization method agreed with the so-called “self-preserving” principle\(^9\). According to this principle, a logarithmic normal distribution is shown, and the agglomerate maintains a constant geometrical standard deviation while it grows. In the solvent change method, small agglomerates (<12 μm) were found to exist in fairly large proportions with large agglomerates (100 ~ 300 μm) at the initial stage of the agglomerated crystallization, but small agglomerates were seen to exceed large agglomerates as the agglomeration progressed. On the other hand, scarcely any change was observed in the maximum diameter of the agglomerates.

With a view to clarifying the agglomeration mechanism of the crystals in each of the two methods, the behavior of crystals was examined in the crystallization where no bridging liquid
was used. Most of the crystals produced by the two methods were of sizes up to several μm, as shown in Fig. 4, but particles as large as 100 ~ 300 μm were also seen to exist in the solvent change method. Scanning electron microscopy [Figs. 10 (a) and (b)] showed them to be agglomerates of fine crystals. No such agglomerates were seen to exist in the neutralization method. By dropping a DMF solution of phenytoin into the water in a petri dish, it was possible to examine how crystals precipitated and gathered [Fig. 10 (c)]. As soon as the liquid drop touched the surface of the water, a crystal cluster resulting from solid-based cross-linking was formed and fell to the bottom. Furthermore, fine crystals precipitated at the surface of the water as the DMF spread. At first, this clustering mechanism was considered to be due to localization of DMF at the surface of the precipitated phenytoin crystal and to the function of the localized DMF as a bridging liquid. However, this assumption was disproved by the facts that, 1) the concentration of DMF in bulk showed no difference whether phenytoin was present or not, 2) phenytoin dispersed in water did not agglomerate when DMF was added, and 3) when the crystallization solvent already contained DMF, the solubility of phenytoin increased, the recovery of the clusters decreased and, furthermore, the average diameter of the crystal clusters decreased [Fig. 11 (a)]. Figure 11 (b) shows the relationship of the loading weight of phenytoin in DMF to the recovery of the crystal clusters and their average diameter. As the concentration of phenytoin in DMF was increased, the recovery and average diameter of the crystal clusters increased accordingly. On the other hand, the crystals which precipitated formed no cluster when exposed to ultrasonic waves. These results show that when stirring is weak, a new crystal nucleus is formed among precipitated crystals before they are dispersed, and the crystal nucleus acts as a bridging solid among the crystals to form a crystal cluster.

With respect to friability, agglomerates of crystals obtained by using a bridging liquid were compared with clusters of crystals obtained without using any bridging substance, the results being shown in Fig. 12. The specimens were of sizes ranging from 250 to 270 μm. The comparison clearly showed the clusters to be much firmer than the agglomerates. This
corroborated the observation that crystals clustered by solid-bridging. From the results shown in Fig. 5, it was learned that the agglomerates obtained by the solvent change method gradually became more difficult to pulverize as the pulverization progressed. In connection with this, the results of the comparison in Fig. 12 suggests the presence of a hard cluster in the interior of such an agglomerate which resulted from solid-bridging at the initial stage of agglomeration.

Considering the above-mentioned results, the agglomeration mechanisms of crystals in the two methods may be reduced to the diagrams shown in Fig. 13. In the neutralization method, agglomeration takes place by the coalescence mechanism which is based on a bridging liquid, whereas agglomeration developed by the sol-
Neutralization method

Solvent change method

Agglomeration coalescence

layering

Fig. 13 Schematic internal structure of agglomerate and mechanism of agglomeration

The consolidation of agglomerated crystals

The agglomeration mechanism of particles in agglomerated crystallization consists of the growth of an agglomerate which, as is now clear, allows the bridging liquid to exude from the interior to the surface under pressure of consolidation and becomes tied to another particle by forming a liquid bridge. It is important, therefore, to analyze the process of consolidation of agglomerated crystals when the process and rate of the agglomeration are considered.

Figure 14 shows the relationship between the particle size and the apparent density of the agglomerates determined by a microscopic technique. With respect to agglomerates obtainable in the neutralization method, a positive correlation was shown to exist between the two scales; that is, it is seen that by the neutralization method the agglomerates grow by coalescence while they undergo consolidation. With respect to agglomerates obtainable by the solvent change method, however, no clear relationship was shown to exist between the particle size and the apparent density, probably because a mixed model of coalescence and layering, as described earlier, controlled the growth mechanism of the agglomerates.

Next, the process of consolidation was analyzed with respect to agglomerates in the neutralization method, which showed a correlation between the particle size and the apparent density. The total weight $W$ of the precipitated crystals is expressed by the following equation,

$$W = \frac{\pi}{6} \cdot l^3 \cdot \rho_{ap} \cdot N$$

where $\rho_{ap}$ is the apparent density of the agglomerate, and $N$ is the total number of ag-

![Fig. 14](image-url)
glomerates in the system. The crystallization ended as soon as an alkali solution of phenytoin was introduced into the system. $W$ remained unchanged during agglomeration. $N$ is expressed by Eq. (7) and $l$ is expressed by Eq. (4), as shown before, so that Eq. (8) can be formed from Eq. (4), (6) and (7).

$$N = N_0 \cdot \exp \left[ -k_3 t \right] \quad (7)$$

$$\frac{1}{\rho_{ap}} = \frac{\pi l_0^2 N_0}{6W} \cdot \exp \left[ (3k_1 - k_3) t \right] \quad (8)$$

**Figure 15** shows the relationship between $\ln(1/\rho_{ap})$ and $t$. The data formed straight lines so that Eq. (8) was satisfied. Accordingly, it has become clear that the incline of each straight line (consolidation rate constant of agglomerates) was dependent upon the agglomeration rate constants $k_1$ and $k_3$.

4. Conclusion

The results of the present study can be summarized as follows:

1) Agglomerated crystallization techniques, i.e., neutralization and solvent change techniques, which enable the primary and secondary properties of phenytoin crystals to be simultaneously controlled and as desired, were devised as novel particle-design techniques. The methods were capable of producing free-flowing agglomerates of high mechanical strength composed of fine phenytoin crystals.

2) The differences between the two methods in the agglomeration mechanism of phenytoin crystals were clarified. It was determined that whereas it was the coalescence mechanism by liquid-bridging that controlled the agglomeration of crystals in the neutralization method, clusters of crystals were formed by solid-bridging at the initial stage by the solvent change method, and the agglomeration developed into a concurrence of the clustering and layering agglomeration in which fine crystals agglomerated on the surface of the cluster by liquid-bridging. As a result, the agglomerates developed by both methods were shown to differ in the manner in which they were pulverized. The agglomerates developed by the solvent change method had a hard nucleus formed by solid-bridging in the interior, so that they were relatively hard to pulverized compared with the agglomerates developed by the neutralization method.
3) Whereas the agglomerates in the neutralization method showed a positive correlation between particle size and apparent density, the agglomerates developed by the solvent change method showed no such relationship because of the difference in the agglomeration mechanism. It became clear that the rate of consolidation of the agglomerates of crystals in the neutralization method was dependent upon the agglomeration rate constants in the crystallization.

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Nomenclature

\[ N \] : total number of agglomerate in system \([-]\)
\[ N_0 \] : total number of agglomerate in system at \( t = 0 \) \([-]\)
\[ n \] : impaction number \([-]\)
\[ Pr \] : probability of breakage per impaction \([-]\)
\[ R_n(x) \] : cumulative weight percent over size \( x \) \([\%]\)
\[ t \] : time \([\text{min}]\)
\[ W \] : total weight of crystal precipitated in system \([\text{g}]\)
\[ X \] : pulverized fraction \([-]\)
\[ \rho_{ap} \] : apparent density of agglomerate \([\text{g}\cdot\text{cm}^{-2}]\)
\[ \phi \] : shape factor of agglomerate \([-]\)

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