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Simulation of Agglomeration. II.[1] Two-dimensional Random Addition Model. (1)

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Two-dimensional agglomerates having various degrees of packing were formed by successive addition of uniform discs to a core by means of a Monte Carlo simulation procedure. Whether cohesion between discs occurred or not was determined by comparing the pseudo-random number generated at every collision with the cohesion probability P. The figures of agglomerates formed by this simulation method appear very similar to those of real agglomerates observed under a microscope. The void fraction of agglomerates and the average coordination number were calculated.

Keywords——agglomeration; coagulation; granulation; packing; powder; particle; disc; two-dimensional model; simulation

Granulation is an important process in the pharmceutical industry. Recentry, the wet spherical agglomeration method[3] has attracted particular interest as a new granulation technique. This method involves "agglomeration" or "flocculation" of powder particles in a liquid phase. It has been recognized that the mechanism of agglomeration or floccuration in a liquid phase has many points of resemblance to that of "coalescence" or "coagulation" in colloid chemistry. In the previous work[1b] the agglomeration of particles was simulated by using a two-dimensional coalescence model.

Many studies have been reported of the variables which affect the formation of agglomerates, such as the size and shape of primary particles, the particle–particle interaction, *etc.* Various theoretical and experimental approaches[4] for clarifying the process of agglomeration or coagulation have also been attempted. However, work on the structure or geometry of agglomerates has not been satisfactory. One method of investigating this subject is by simulating the process of agglomeration on a digital computer. Vold[5] presented a three-dimensional agglomeration model and gave projections of the agglomerates formed. A two-dimensional random packing of discs was modeled by Kausch and co-workers.[6] In both models described above, an agglomerate was formed by successive additions of uniformly sized primary particles or discs to a core. Sutherland[7] and Goodarz-nia[8] developed agglomeration models based on cluster additions, where the collision sequences was calculated according to the Smoluchowski equation.

In the present work, the agglomeration process has been simulated by using a two-dimensional model with reference to Kausch's procedure. A major limitation of his model, as well as Vold's model, was that no consideration was given to the control over the cohesion between discs as they collide. Kausch assumed that no cohesion occurred between discs; *i.e.*, upon contact, a disc rolled around the discs already placed so that it always approached the origin until a stable position was reached. In contrast, in Vold's model, it was assumed that particles were always fixed at their first point of contact. In practice, however, various degrees of interaction may exist between powder particles. The present authors have attempted to introduce the concept of cohesion probability into the model to control the cohesion between discs, and agglomerates having various degree of packing have been obtained.

Method

The two-dimensional model reported here consists of the random addition of discs under the influence of a central force. At the start a disc numbered zero (i_0) is placed at the origin. Any disc approaching the origin encounters the central disc or any disc in an agglomerate already present. Fig. 1 shows a typical diagram illustrating the process of agglomeration, where a disc i_9 approaches the origin along the direction θ. θ is selected randomly by means of pseudo-random numbers from zero to 2π. The disc i_9 encounters the disc i_7 in its path at the position (9—1). Whether the disc adheres in this position or not is determined by comparing the pseudo-random number newly generated with a given cohesion probability P. When P is larger than the pseudo-random number the disc is assumed to be fixed in this position. When P is smaller, the disc begins to roll around i_7 so that it approaches the origin. During this rolling procedure it will come into contact with a new disc i_1 at the position (9—2), but this position is not always stable because of the existence of the centripetal force. A pseudo-random number is then generated again and compared with P. If P is smaller than the pseudo-random number the disc begins to roll again around the disc i_1. When the disc i_9 reaches the stable position (9—3) the rolling ends. About 45 discs were added by these procedures to form an agglomerate and the location of each disc was calculated.

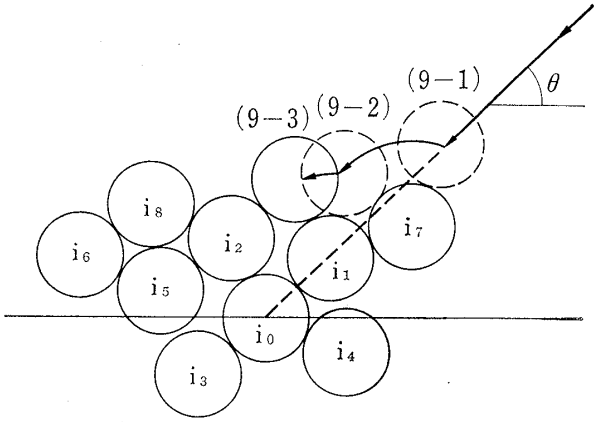


Fig. 1. Procedure of Random Addition of Discs

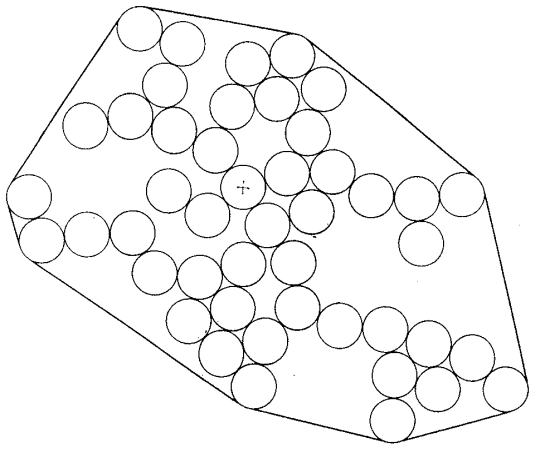


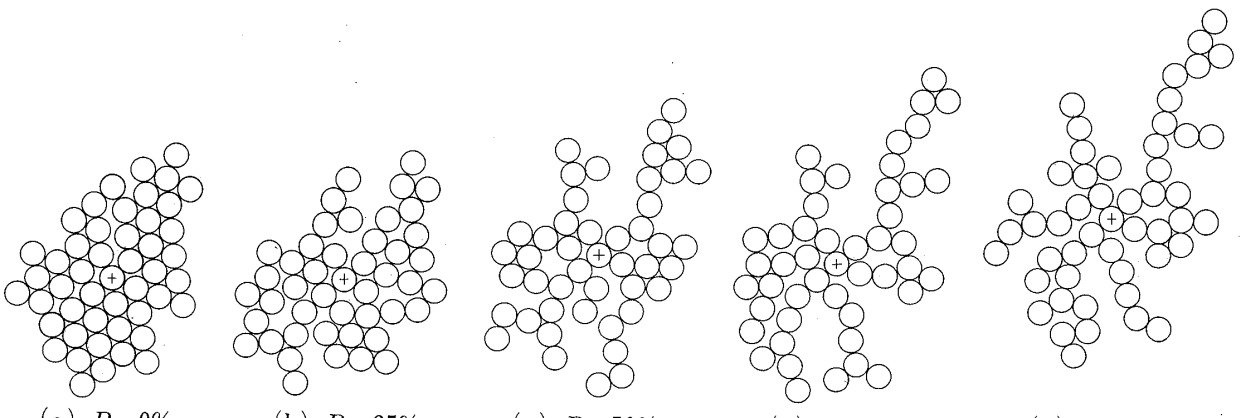
Fig. 2. Determination of the Void Fraction of Agglomerates

The point marked + indicates the origin.

The void fraction (ε) of an agglomerate is defined as the fraction of the area not covered by discs.

$$\varepsilon = 1-(na/A) \qquad (1)$$

where A is the apparent area of an agglomerate, n the number of discs involved in the agglomerate, and a the area of a unit disc. The method of determing the apparent area of an agglomerate is illustrated in Fig. 2. The area surrounded by the thick line, which is drawn as if the agglomerate is tied tightly with a string, is assumed to be A.



(a) $P=0\%$ (b) $P=25\%$ (c) $P=50\%$ (d) $P=75\%$ (e) $P=100\%$

Fig. 3. Typical Figures of Agglomerates obtained by Varying the Cohesion Probability P

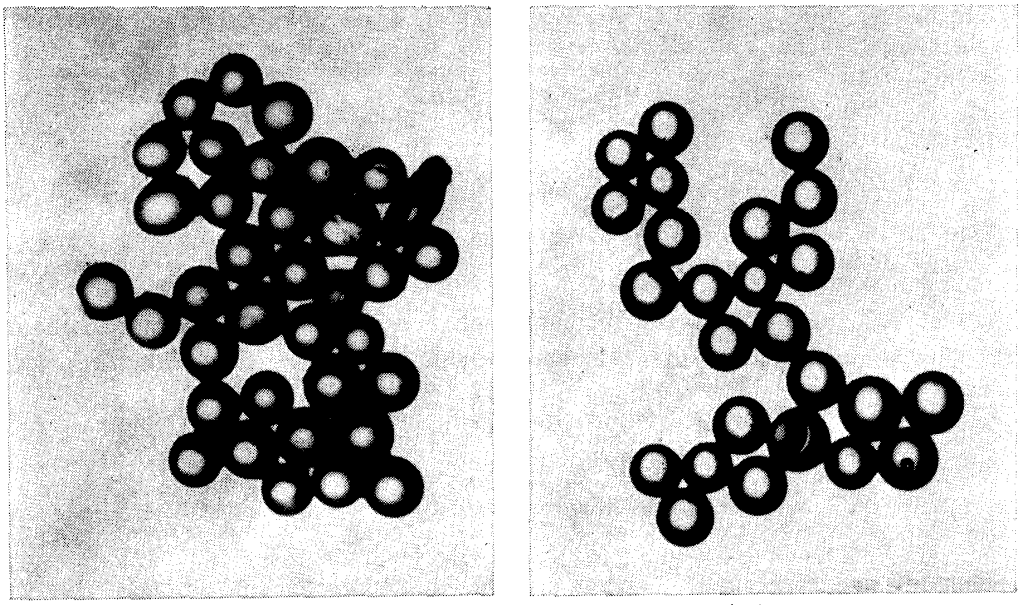


Fig. 4. Microscopic Photographs of Agglomerates formed with Glass Beads

The Values of ε and k obtained from these figures are 0.41 and 3.6 for (A) 0.55 and 2.6 for (B) which are consistent with the results of simulation shown in Fig. 5.

Results and Discussion

Typical figures of agglomerates formed by taking various values of cohesion probability are shown in Fig. 3. All of them have appearances very similar to those of real agglomerates observed under a microscope, such as shown in Fig. 4. These agglomerates were formed from glass beads suspended in carbon tetrachloride containing a small amount of sodium chloride aqueous solution as an agglomerating agent.[3)]

Fig. 5 shows the change of void fraction and average coordination number ($\bar{k}$) with cohesion probability P. ε increases and $\bar{k}$ decreases gradually with increasing value of P.

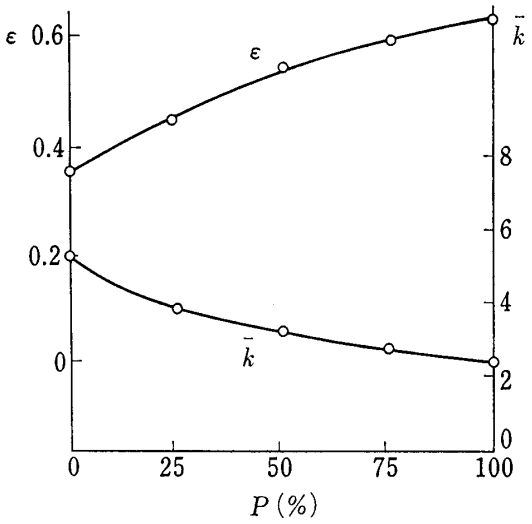


Fig. 5. Void Fraction of Agglomerates and Average Coordination Number as a Function of Cohesion Probability P

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References and Notes

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Effect of Prior Administration of Aminophylline, Caffeine, or Propranolol on the Antitumor Activity of 6-Mercaptopurine or 6-Mercaptopurine Riboside

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The effect of prior administration of aminophylline, caffeine, or propranolol on the antitumor activity of 6-mercaptopurine (6-MP) or 6-mercaptopurine riboside (6-MPR) against Ehrlich solid tumor in ddY male mice was studied. These three drugs each weakened the action of 6-MP but had less effect on the action of 6-MPR. Considering the variation in the activities of hypoxanthine–guanine phosphoribosyltransferase and xanthine oxidase, we suggest that higher doses of aminophylline and propranolol may promote the conversion from 6-MP to biologically inactive thiouric acid or hypoxanthine rather than to biologically active thioinosinic acid.

Keywords——aminophylline; caffeine; propranolol; antitumor activity; 6-mercaptopurine; 6-mercaptopurine riboside; Ehrlich solid tumor; mice; hypoxanthine–guanine phosphoribosyltransferase; xanthine oxidase

6-Mercaptopurine (6-MP) is converted *in vivo* into biologically active thioinosinic acid (TIMP) by hypoxanthine–guanine phosphoribosyltransferase (HGPRTase), or is oxidized to thiouric acid, a noncarcinostatic metabolite, by xanthine oxidase.[1] Recently Higuchi *et al.*[1a,1b] reported that the effects of 6-MP may be modified by drug-metabolizing enzymes in the mouse liver.

In the previous paper,[2] we demonstrated that butoctamide stimulated the HGPRTase activity and inhibited the xanthine oxidase activity of mouse liver, and enhanced the antitumor activity of 6-MP on Ehrlich solid tumor in mice. Thus, the combined use of such drugs with 6-MP may change the activity of drug-metabolizing enzymes in the liver, leading to changes in the antitumor activity of 6-MP.

Aminophylline, caffeine, and propranolol have an effect on cyclic AMP (c-AMP) formation or degradation in cell. Gericke and Chandra[3] reported that c-AMP inhibits the growth of transplanted NKL-lymphosarcoma in mice.

On the other hand, it has been reported by many investigators[4,5] that adenyl cyclase and phosphodiesterase activities and the content of c-AMP in tumor cells are lower than in normal cells. However, the relationship between content of c-AMP and tumor growth is still uncertain.

In this work, we examined the effects of prior administration of aminophylline, caffeine, or propranolol on the antitumor activity of 6-MP or 6-mercaptopurine riboside (6-MPR).

Materials and Methods

Animals——Male ddY mice weighing 20—22 g were used in all experiments.

Drugs——The drugs used were as follows: aminophylline (theophylline ethylenediamine, Neophyllin®, Eisai Co.), caffeine (caffeine and sodium benzoate, Fuso Yakuhin Kogyo Co., was used; doses are expressed