[Chem. Pharm. Bull.
30(2) 666—672 (1982)]

# Mixing of Pharmaceutical Powders and Granules. II.[1] Mixing Degree of Granules and Various Kinds of Powders

HIROSHI FUJIWARA, SUSUMU KAWASHIMA,* and SACHIKO OMURA

*School of Pharmacy, Hokuriku University, Kanagawa-machi,
Kanazawa 920-11, Japan*

(Received June 22, 1981)

The mixing degree between granules and various kinds of powders was investigated based on the assumption that it could be treated similarly to the pure granule system described in the previous paper. The theoretical mixing degree of the target particles for complete mixing was determined by assuming that it could be calculated from the arbitrary content of each particle and the grain size distribution.

Experimental values of mixing degree obtained by using various kinds of powders, such as talc, synthetic aluminium silicate, magnesium oxide and lactose, and granules were in good agreement with the theoretical results. These theoretical mixing degrees may be useful as an indication of the limits of practical mixing of powders and granules.

**Keywords**——mixing of powders and granules; analysis of grain size; determination of mixing degree; complete mixing state; measurement of apparent and true density; target particle; randomized mixing; ordered mixing; grain size distribution

Because of their poor miscibility, granules and powders are packed separately for dispensing, although in general, they are mixed together for the manufacture of tablets. Therefore, mixing plays an important role in the preparation of such solid dosage forms. Consequently, the quality of pharmaceutical dispensing is affected by the limit of mixing degree of granules and powders.

In a previous paper,[1] the mixing of two kinds of granules with different grain sizes was investigated to provide a basis for developing a theoretical equation for the mixing limit. The theoretical values were compared with the observed ones.

In the mixing of granules and powders, a similar treatment seemed to be possible. The mixing degrees for several kinds of powders and granules were measured in the same way as those of pure powders. Theoretical equations are proposed in this paper to explain the results.

## Experimental

**Powders**——Talc, synthetic aluminium silicate, magnesium oxide and crystallized lactose of J.P.IX grade were used.

**Preparation of Granules**——Granules were prepared by the wet granulation method described in the previous paper and the grain size distribution was analyzed to obtain the statistical values as shown in Table I.

In place of tartradin, salicylic acid was used as the tracer for mixing the granules with magnesium oxide.

**Analysis of Grain Size in Powders**——Grain size was determined with a Shimadzu sedimentograph, type SA-2. The dispersing media for talc and magnesium oxide were 0.2% and 0.3% aqueous solutions of sodium hexametaphosphate, respectively. Dioxane was used as the dispersing medium for lactose which is soluble in water, but a mixture of glycerine and water with hexametaphosphate aqueous solution (0.3%) was used for synthetic aluminium silicate to give wettability.

**Determination of Intraparticle Porosity in Granules**——A mixture of paraffin (40 g) melted in a Kjeldahl-type flask at 80°C and granules (10 g) was evacuated to *ca.* 1 mmHg during 2 h to allow the paraffin to penetrate into the intrapaticle void of the granules. The penetrated paraffin was extracted with ether in a Soxhlet extractor after removal of excess paraffin on the granule surface by means of a filter paper. The weight of paraffin was converted to the volume, and the intraparticle void of the granules[2] was estimated to 0.49 ml/g (mean of three measurements) by considering the volume of paraffin as being equivalent to the intraparticle void volume.

**Determination of Porosity in Mixture**——The true and apparent densities were determined with a Beckman air comparison pycnometer, model 930, and by the tapping method, respectively. The apparent density was calculated from the constant volume obtained by tapping a graduated cylinder (100 ml) filled with granules or powder, or a mixture of the two (40 g).

The porosity can be defined as

$$\text{porosity} = 1 - \frac{d_{\text{pap}}}{d_{\text{p}}M_{\text{W}} + d_{\text{g}}(1 - M_{\text{W}})} \tag{1}$$

where $d_{\text{pap}}$ is the apparent density of powder, $d_{\text{p}}$ and $d_{\text{g}}$ are the true densities of powder and granules, respectively, and $M_{\text{W}}$ is the mixing ratio by weight.

**Determination of Mixing Degree**——Mixing degree was measured as described in the previous paper. Ten samples (1 g each) were weighed out individually after thorough mixing of the mixture of granules and powder (40 g). Each sample was dissolved in water to remove insoluble materials, and then the concentration of tartradin in the filtrate was measured by spectrophotometry. However, when talc was used, the supernatant obtained after removing the bulk of the talc by centrifugation at 1500 rpm for 30 min, was filtered, because of the poor efficiency of usual filtration.

In addition, when magnesium oxide was mixed, salicylic acid was added as the tracer to overcome the difficulty in measurement caused by the decoloration of tartradin during mixing. Salicylic acid was determined by spectroscopic analysis at 296 nm of the mixture in carbonate buffer (0.1 M, pH = 10.0) after treatment as in the case of talc. Since salicylic acid was successfully extracted from the mixture with the buffer, magnesium oxide had no influence on the measurement.

The weight ratio of granules in each mixture was calculated from the calibration curve to obtain the standard deviation.

## Results and Discussion

In the mixing of two kinds of particles,[3] the random pattern where the arrangement of both particles has no regularity is said to be the mixing limit and is defined as the complete mixing state. However, some regularity is presumed to occur at any mixing ratio in the case of particles with extremely different sizes, such as granules and powders, and it is known that the change of porosity decreases continuously to the minimum value with increasing mixing ratio in such mixing systems.[4]

This may be because the small particles exist only the voids between large particles in a mixture of a large amount of large particles and a small amount of small ones, although large particles exist at random in a mixture having the reverse ratio. Therefore, since the positions of the target particles are restricted by the mixing ratio and the porosity is changed by the arrangement of the particles, the arrangement of the target particles which gives the best approach to the complete mixing state can be estimated from the porosity of the mixture. Thus, the porosity of various mixtures was first measured.

Fig. 1, a—d shows plots of the porosity (%) of mixtures containing granules and powder, such as talc, against the mixing ratio. In every case, the minimum value was obtained at a definite mixing ratio, as expected. When the amount of granules is greater than that of powder, the theoretical equation for porosity is given by Eq. 2, assuming that the packing of the granules is not altered by the addition of powder.

$$\text{porosity} = \frac{(1-M_{\text{W}})/d_{\text{gap}} - (1-M_{\text{W}})/d_{\text{g}} - M_{\text{W}}/d_{\text{p}}}{(1-M_{\text{W}})/d_{\text{gap}}} \tag{2}$$

On the other hand, when the amount of powder is more than that of granules, granules are supposed to be dispersed in the mixture and it is assumed that the state of the powder is not changed by the mixing ratio of granules; it is further assumed that the powder does not enter the intraparticle void volume of the granules.

In such a packing structure, the void volume of the mixture is equal to the sum of the void volume due to the packing conditions of the powder and the intraparticle void volume of the granules. The theoretical equation for porosity is given by

$$\text{porosity} = \frac{\{M_{\text{W}}/d_{\text{pap}} + (1-M_{\text{W}})/d_{\text{g}} + (1-M_{\text{W}})P'\} - \{M_{\text{W}}/d_{\text{p}} + (1-M_{\text{W}})/d_{\text{g}}\}}{M_{\text{W}}/d_{\text{pap}} + (1-M_{\text{W}})/d_{\text{g}} + (1-M_{\text{W}})P'} \tag{3}$$

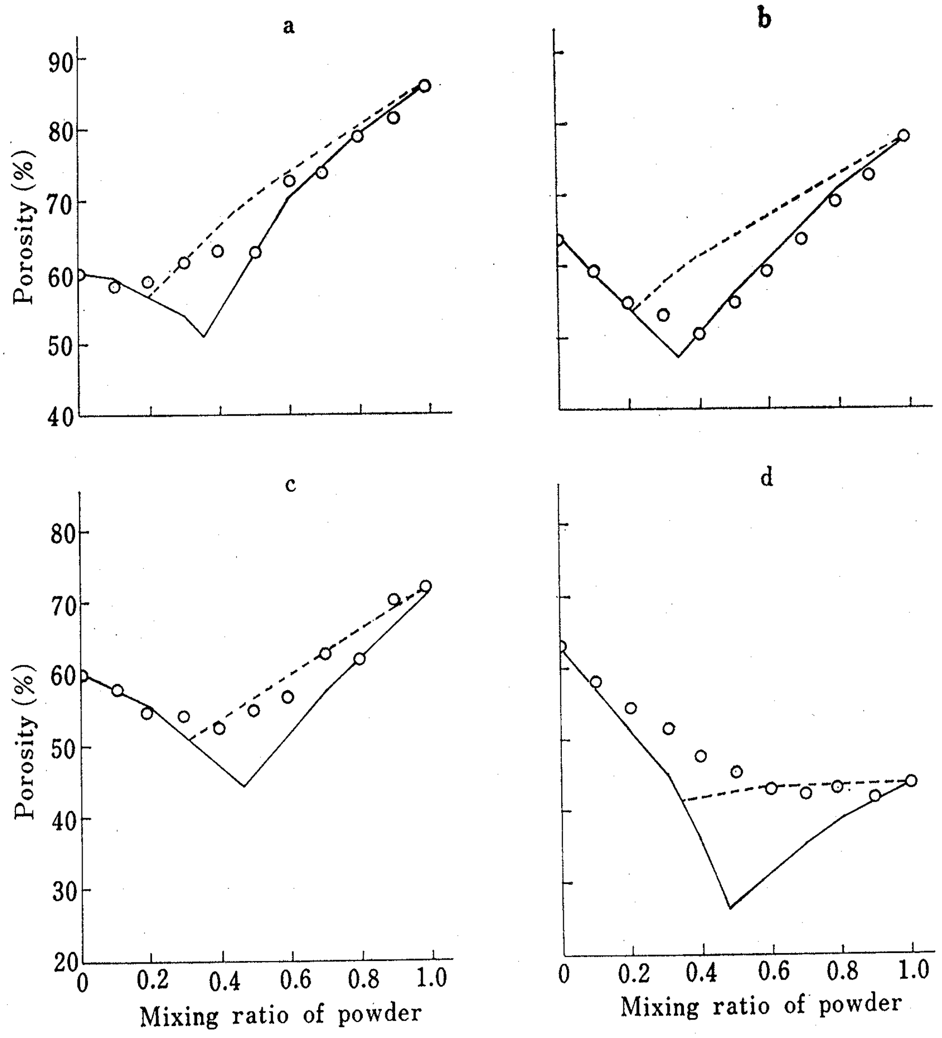

Fig. 1. Porosity of Powder Mixtures with Granules

○, observed value; —, calculated curve from Eqs. (2) and (4); ---, calculated curve from Eq. (3); a, magnesium oxide; b, synthetic aluminium silicate; c, talc; d, crystallized lactose.

TABLE I. Statistics of Particle Size Distribution for Granules

| | |
|---|---|
| Mean number in 1 g granules | 3802.3 |
| Standard deviation in number ($\sigma_{NG}$) | 584 |
| Mean weight ($W_G$) | $2.36\times10^{-4}$ g |
| Standard deviation in weight | $3.25\times10^{-5}$ g |

where $P'$ is the ratio of the intraparticle void volume to the apparent volume per weight of the granules. It was determined to be 0.318 from the observed data on intraparticle porosity of the granules. If the grain size of powder is sufficiently smaller than the pores which constitute the intraparticle void of the granules, the powders may also enter the intraparticle void. In this case, the porosity is given by Eq. 4.

$$\text{porosity}=\frac{\{M_W/d_{\mathrm{pap}}+(1-M_W)/d_g\}-\{M_W/d_p+(1-M_W)/d_g\}}{M_W/d_{\mathrm{pap}}+(1-M_W)/d_g} \qquad (4)$$

In this equation, the packing condition of powder entering the intraparticle void of granules is supposed to be the same as that of the powder itself.

On this basis, the porosity must show a minimum value when the powder is packed into the void of granules without altering the packing conditions of the granules.

The porosity values calculated by means of Eqs. 2 and 4, and Eq. 3 are plotted in Fig. 1, a—d, with solid and dashed lines, respectively.

The above description seems reasonable, since the observed values of porosity are in good agreement with the theoretical ones. Results found at mixing ratios of 0.4 to 0.5 for magnesium oxide and synthetic aluminium silicate are the only exceptional cases. Further, under conditions where granules are dispersed in powder, it is suggested that the powder also enters the intraparticle void of the granules. In addition, the observed values are greater than the theoretical ones in the vicinity of the minimum point on the theoretical porosity curve.

This phenomenon is thought to be due to the large apparent grain size of granules caused by the effects of ordered mixing produced by the adhesion of powder to the surface of granules. In the case of talc, the observed porosity fitted the theoretical curve calculated from Eq. 3 in the large mixing ratio region of powder.

Thus, this suggests that powder never enter the intraparticle void of the granules owing to the large apparent grain size resulting from the interactive adhesion of talc.

At mixing ratios of above 0.6, crystallized lactose shows behavior similar to that of talc. It is considered that the entry of crystallized lactose into the intraparticle void of granules is again inhibited because of the large grain size.

The packing is affected by the mixing ratio in mixtures of powders and granules, and some regularity is observed in the arrangement of particles. When powders exist only in the void volume of granules, the factors affecting the mixing degree of the target particles in theoretical mixing are the grain size distribution and the probable arbitrary existence in preferred regions of space.

As described previously, the effect of grain size distribution on the mixing degree is reflected in the variation of the particle number per weight. The mean diameter and standard deviation of powders determined by the analysis of grain size, and the average weight and the variation of particle number per weight calculated by assuming spherical form of the particles of powder, are shown in Table II.

TABLE II. Statistics of Size Distribution for Various Powders

| | Mean diameter ($\mu$) | Standard deviation of diameter ($\mu$) | Mean weight of particle ($W_P$, g) | Standard deviation on particle number in 1 g ($\sigma_{NP}$) |
|---|---|---|---|---|
| Talc | 10.69 | 5.13 | $1.80\times10^{-9}$ | $6.13\times10^{7}$ |
| Aluminium silicate | 18.29 | 9.36 | $6.76\times10^{-9}$ | $1.98\times10^{7}$ |
| Magnesium oxide | 1.81 | 0.27 | $1.11\times10^{-11}$ | $3.18\times10^{8}$ |
| Lactose | 32.43 | 18.97 | $2.74\times10^{-8}$ | $7.32\times10^{6}$ |

Since the target particles exist only in the void of granules on mixing, the particles of powder exist at random in the void under the complete mixing condition. Thus, if the powder is packed into the void, the target particles are mixed completely in the packed powder with a random arrangement. Therefore, the theoretical mixing degree can be calculated by estimating the void space and the particle number ($\alpha$) packed in the void, by means of Eqs. 5 and 6, respectively. However, the packing condition of the powder into the void is almost the same as that of the powder itself, as shown in Fig. 1, a—d.

$$\text{void space} = (1-M_W)\left\{\frac{1}{d_{\text{gap}}}-\frac{1}{d_g}\right\}W \qquad (5)$$

$$\alpha = \frac{(1-M_W)}{W_P}\left\{\frac{1}{d_{\text{gap}}}-\frac{1}{d_g}\right\}d_{\text{pap}}\cdot W \qquad (6)$$

Here, $\boldsymbol{W}$ is the sample weight and $\boldsymbol{W}_{\mathrm{P}}$ is the average particle weight of powder. The variation ($\sigma^2{}_{OP}$) based on the random mixing of powder is calculated as follows.

$$\sigma^2_{OP} = \frac{\boldsymbol{M}_{\mathrm{W}}}{\boldsymbol{W}_{\mathrm{P}}}\left\{1-\frac{\boldsymbol{M}_{\mathrm{W}}}{\alpha\cdot\boldsymbol{W}_{\mathrm{P}}}\right\}\boldsymbol{W}^2 \tag{7}$$

Then, the expected value ($\sigma^2{}_W$) of the variation in weight ratio for complete mixing can be expressed by

$$\sigma^2{}_W = \frac{\boldsymbol{M}_{\mathrm{W}}{}^2\sigma^2_{NP}+\sigma^2_{OP}}{\boldsymbol{W}^2}\cdot\boldsymbol{W}_{\mathrm{P}}{}^2 \tag{8}$$

If the granules are dispersed into the powder, under the ultimate mixing conditions the target granules exist at random in the volume formed by the mixture system. Therefore, the volume of the mixture system and the number of granules packed into the volume, $\beta$, are by given Eqs. 9 and 10, respectively.

$$\text{void space} = \left\{\frac{\boldsymbol{M}_{\mathrm{W}}}{d_{\mathrm{pap}}}+\frac{1-\boldsymbol{M}_{\mathrm{W}}}{d_{\mathrm{g}}}\right\}\boldsymbol{W} \tag{9}$$

$$\beta = \left\{\frac{\boldsymbol{M}_{\mathrm{W}}}{d_{\mathrm{pap}}}+\frac{1-\boldsymbol{M}_{\mathrm{W}}}{d_{\mathrm{g}}}\right\}\frac{d_{\mathrm{gap}}}{\boldsymbol{W}_{\mathrm{G}}}\cdot\boldsymbol{W} \tag{10}$$

Here, $\boldsymbol{W}_{\mathrm{G}}$ is the mean granule weight.

Since the complete mixing conditions are thought to be those under which the target granules exist at random in the volume, the variation of the mixing degree, $\sigma^2{}_{OG}$, can be defined Eq. 11.

$$\sigma^2{}_{OG} = \frac{(1-\boldsymbol{W}_{\mathrm{W}})}{\boldsymbol{W}_{\mathrm{G}}}\left\{1-\frac{1-\boldsymbol{M}_{\mathrm{W}}}{\beta\cdot\boldsymbol{W}_{\mathrm{G}}}\right\}\boldsymbol{W}^2 \tag{11}$$

Thus, the expected weight variation is given by Eq. 12.

$$\sigma^2{}_W = \frac{(1-\boldsymbol{M}_{\mathrm{W}})^2\cdot\sigma^2_{NG}+\rho^2_{OG}}{\boldsymbol{W}^2}\,\boldsymbol{W}_{\mathrm{G}}{}^2 \tag{12}$$

Furthermore, when the powder is packed densely into the void of the granules, that is, the porosity is minimum, it is considered that the particles are mixed completely. In this case, the expected value of weight variation for complete mixing is as follows.

$$\sigma^2{}_W = \frac{\{\boldsymbol{M}^2{}_{\mathrm{W}}\cdot\sigma^2_{NP}+(1-\boldsymbol{M}_{\mathrm{W}})^2\cdot\sigma^2_{NG}\}\,\{\boldsymbol{M}_{\mathrm{W}}\cdot\boldsymbol{W}_{\mathrm{P}}+(1-\boldsymbol{M}_{\mathrm{W}})\cdot\boldsymbol{W}_{\mathrm{G}}\}^2}{\boldsymbol{W}^2} \tag{13}$$

In the experiments with mixtures containing granules and additives, the observed values of mixing degree at various mixing ratios are shown in Fig. 2a, 2b, 2c and 2d for talc, synthetic aluminium silicate, magnesium oxide, and crystallized lactose as additives, respectively. Data were obtained in triplicate under given experimental conditions and plotted against the mixing ratio.

The theoretical mixing degree can be calculated from Eqs. 8, 12 and 13 for the various mixing ratios of powder and granules. The parameters used for calculation, $\sigma_{NP}$, $\sigma_{NG}$, $\boldsymbol{W}_{\mathrm{P}}$ and $\boldsymbol{W}_{\mathrm{G}}$, are shown in Table I and II. In Fig. 2 the theoretical values calculated from Eq. 11, and Eqs. 7 and 12 are represented by solid and dashed lines, respectively. As shown in Fig. 2, the mixing degrees of talc, synthetic aluminium silicate, and crystallized lactose with granules show similar behavior, and the observed values agree approximately with the theoretical ones. Under the conditions of "powder in granule" mixing, the values differ slightely, but $\sigma^2{}_{NP}$ in the theoretical equation is the value based on the assumption that the grain size of powder shows a normal distribution, and in practice the grain size distribution frequently deviates from normality.

In the mixing of magnesium oxide and granules, the calculated standard deviation under

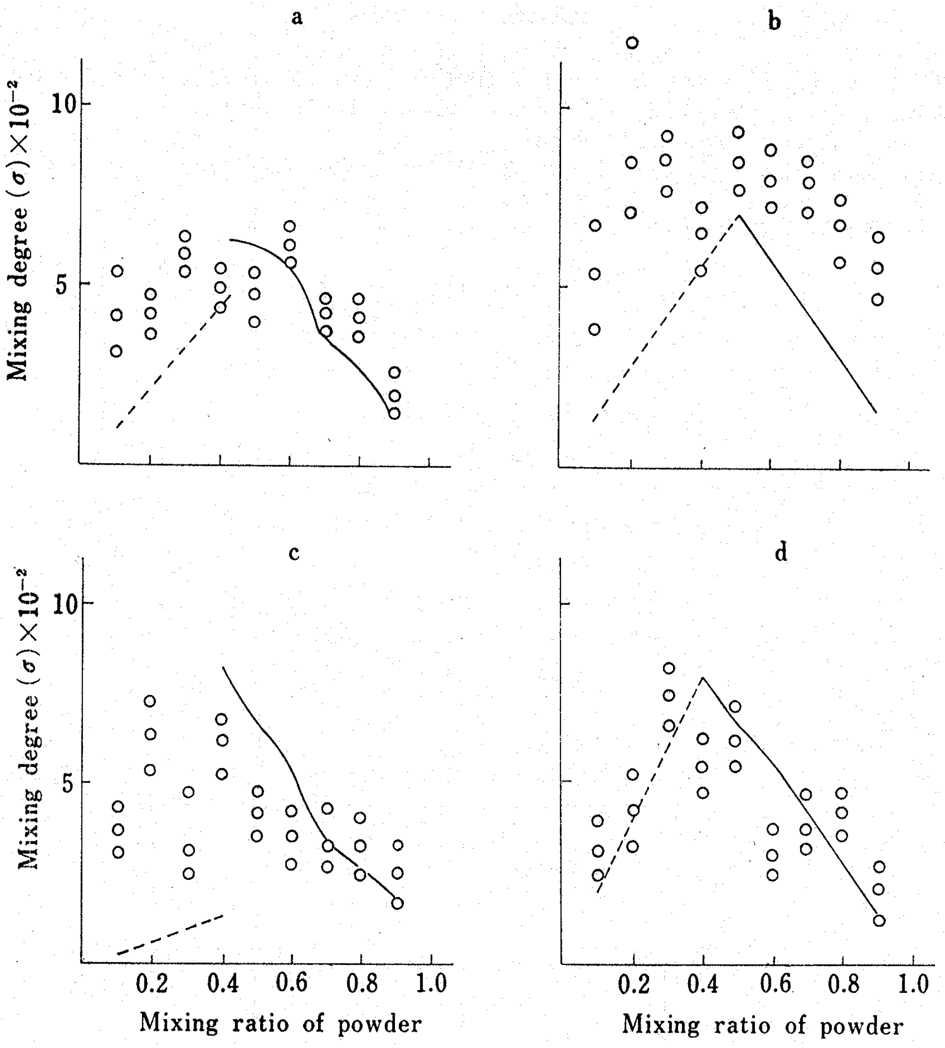

Fig. 2. Mixing Degree of Powders with Granules

○, observed value; —, calculated curve from Eq. (11); ----, calculated curve from Eqs. (7) and (12); a, talc b, synthetic aluminium silicate; c, magnesium oxide; d, crystallized lactose.

"powder in granule" conditions is smaller than that with other additives, although very different from the theoretical curve under "granule in powder" conditions.

The difference from other powder arises because the mean particle weight, $W_P$ is smaller than that of other powders, and is apparent even in the aggregation behavior. In practice, the width of the grain size distribution seems to become larger. These factors may account for the abnormality of the calculated value.

Further, the effect of interparticle interaction between powder and granules on mixing, such as ordered mixing,[5] must be considered in each case. However, since the variation of porosity against mixing ratio is in reasonable accord with the theoretical equation, these interactions seem not to affect the mixing degree, at least in the present cases.

The theoretical mixing degree was calculated by assuming that the mixing degree of the target particle under the complete mixing conditions between powder and granules is determined by the relative amounts of the particles and their grain size distributions. The validity of these assumptions was supported by the finding that the calculated values are generally in good agreement with the observed ones. Thus, the present theoretical considerations should be of some use for predicting the mixing degrees of powders and granules in practical pharmaceutical processing.

## References and Notes

1) Part 1: H. Fujiwara, S. Kawashima, and S. Omura, *Chem. Pharm. Bull.*, **30**, 266 (1982).
2) H. Fujiwara, J. Toda, and M. Kato, *Chem. Pharm. Bull.*, **14**, 601 (1966).
3) P.M.C. Lacey, *J. Appl. Chem*, **4**, 154 (1954).
4) E. Managold, R. Hofmann, K. Solf, *Kolloid Z*, **56**, 142 (1932); D.R. Hudson, *J. Appl. Chem*, **20**, 154 (1947).
5) J.A. Hersey, *Powder Technology*, **11**, 41 (1975).