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Mechanochemical Considerations on the Numbers of Radicals generated in Binary Powders of Glycolic Acid and Silica-Alumina and of Potato Starch and Silica-Alumina

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The numbers of radicals generated in binary powders of glycolic acid and silica-alumina and of potato starch and silica-alumina determined by means of electron spin resonance (ESR) were found to be affected by mechanical energies. For example, the number of spins increased with increase in the shaking duration, with increase in the compressive stress, and with decrease in the size of particles. The numbers of radicals were also influenced by the techniques used for mixing the binary powders. An increase in the number of radicals induced by mechanical forces may increase the rates of chemical reactions during the manufacture and storage of drugs.

Keywords——ESR; radical; mechanochemistry; glycolic acid; potato starch; silica-alumina; shaking; compressive stress; solid acid

Mechanochemistry is concerned with the physical and chemical changes in the properties of materials due to the mechanical forces applied to organic or inorganic solids, powders, and liquids. Specifically, it includes the effects of sintering, lubrication, wear, adsorption, wetting, cracking, structural changes, and chemical reactions, such as oxidation, reduction, decomposition, polymerization, and corrosion.[1] These transformations are usually preceded physically by variations of surface structures and chemically by the ejection of electrons, the formation of ion pairs, the cleavage of covalent bonding, or the local formation of high energy sites, due to the energy or the heat evolved in the materials in the course of mechanical processes, such as mixing, grinding, compressing, cutting, polishing, lubricating, and working.[1] Mechanochemical changes can also be caused by exposing materials to X-rays, γ-rays, light, or ultrasonic radiation.[1] In the field of engineering, significant amounts of experimental data have been accumulated in recent years in a wide variety of engineering processes, and have gradually been utilized for practical purposes.

In the field of pharmaceutical sciences, however, almost no attention has been paid to mechanochemistry. As a matter of course, mechanical forces are very frequently applied to powder particles in the manufacture of solid drugs, such as powders, granules, capsules, pills, and tablets. These mechanical energies can alter the physical and chemical properties of the drugs. For example, powders of quartz[2,3] and kaolinite[4,5] ground for different periods display different solubilities in acidic or basic aqueous solutions. Similarly, it seems reasonable to assume that antacids, including powders of aluminosilicates, show different effects in the stomach due only to mechanochemical effects. At the present stage, it seems to be of great importance to accumulate data on the acceleration of chemical reactions in drugs due to mechanical energies and on the mechanochemical modifications of the physical properties of powdery drugs in the course of unit operations such as comminution, mixing, shaking, classification, granulation, tabletting, and so forth.

We described previously the formation of stable radicals in binary powders of a saccharide and a metal oxide,[6,7] and of a metal oxide and an organic compound[8] simply upon vigorous stirring in a glass vessel. Furthermore, we have observed recently that the numbers of radicals in binary powders of glycolic acid and silica-alumina (abbreviated hereafter as GA and SA, respectively) and of potato starch (abbreviated as PS) and SA increased with increase in the

shaking duration, with increase in the compressive stress, and with decrease in the particle size. Thus, the object of this work was to explore the effects of some mechanical processes on the amounts of radicals and to confirm the need for detailed investigations on the mechanochemical modifications of drugs.

Experimental

Materials——Commercial GR grade GA was used after being recrystallized from water and dried under a vacuum. EP grade PS was dried *in vacuo* for 1 h prior to use. Nikki Kagaku N631-L Type SA (150—200 mesh) was calcined for 5 h at 200°C, 400°C, or 600°C (abbreviated henceforth as SA_{200}, SA_{400}, or SA_{600}, respectively).

ESR Measurement——ESR spectra of the powders of SA and GA and of PS and SA were obtained in air with a JES-FE3X type spectrometer (X band, 100 kHz modulation) equipped with a JES-VT-3A2 variable temperature controller and a JES-UCT-2AX variable temperature adapter with the following instrumental settings: power, 20 mW; modulation amplitude, 6.3 G; scan rate, 31.25 G/min; time constant, 3 sec; gain, 2×1000; temperature, 25°C. A signal having $g=2$ was observed at 3285 G with our machine. Amounts of spins in the binary powder of SA and GA were calculated with the aid of calibration curves obtained from the observed spectral intensities of SA impregnated with a standard radical ((diphenyl-picryl hydrazide) DPPH)[9,10] and were converted to numbers of spins per gram of anhydrous SA, whereas the numbers of radicals in the binary system of PS and SA were determined with the aid of calibration curves obtained from the ESR spectra of PS powder impregnated with DPPH[9] with the same instrumental settings as described above and were converted to numbers of radicals per gram of anhydrous PS. The lower limit of detection of radicals was found to be 1×10^{12} spins/g. Experimental errors in the determination of the number of radicals depend on the reproducibility and the S/N ratio of an ESR spectrum, the scatter of the numbers of spins in calibration curves due to the instability of the standard radical on the surface of SA, the powderiness and the size (10—30 mg) of samples used for measuring ESR spectra, and so forth. Errors were found to be at most 3.5% for the binary powder of GA and SA, and at most 9% for the binary powder of PS and SA.

Procedure——Either 10 wt% of GA and 90 wt% of SA, or 99 wt% of PS and 1 wt% of SA were mixed together in air and were shaken vigorously in a glass vessel for 5—240 min.

A mixed powder either of GA and SA or of PS and SA was placed between two stainless steel plates after having been shaken for 15 min in a glass vessel. Compressive stress in the region of 1—500 kg/cm^2 was applied for 5 min by the use of a tabletting machine.

Generally speaking, the intensity of the ESR spectrum of the mixed powder of PS and SA increased for about 24 h after mixing.[6] Meanwhile, as will be described in detail in a subsequent paper, the intensity of the ESR spectrum of the mixed powder of GA and SA increased at most for 170 h after mixing. Therefore, for routine work, the binary powder of GA and SA was allowed to stand in air for 170 h and that of PS and SA was left in air for 24 h after shaking or after compressing, and then their ESR spectra were recorded.

Results and Discussion

Effect of Shaking Duration on the Number of Radicals

Binary System of Glycolic Acid and Silica-Alumina——Table I lists the effect of shaking duration on the number of radicals generated in the binary system of GA (10 wt %) and SA calcined at 200°C, 400°C, or 600°C. It can be seen from Table I that the number of radicals increases with increase in the shaking duration and with increase in the calcination temperature of SA. Furthermore, the increase in the number of radicals becomes smaller with increase in the shaking time, and finally the number of radicals reaches an almost constant value ($\sim87\times10^{15}$ spins/g). The constant level for the binary powder of GA (10 wt %) and SA_{200}, SA_{400}, or SA_{600} was attained at a shaking time of about 720, 300, or 240 minutes, respectively.

Binary System of Potato Starch and Silica-Alumina——The effect of shaking duration on the number of radicals generated in the binary system of PS and 1 wt % of SA calcined at 200°C, 400°C, or 600°C is given in Table II. As can be seen from Table II, the number of spins also tends to increase with increase in the shaking duration and with increase in the calcination temperature of SA. Moreover, the increase in the number of spins gradually becomes smaller with increase in the shaking time, and finally the number of spins becomes

Table I. The Effect of Shaking Duration on the Number of Spins/g in the Binary System of Glycolic Acid (10 wt %) and Silica-Alumina[a]

Shaking duration (min)	Silica-alumina		
	SA_{200}[b] ($\times 10^{15}$ spins/g)	SA_{400}[c] ($\times 10^{15}$ spins/g)	SA_{600}[d] ($\times 10^{15}$ spins/g)
5	11	26	32
15	21	42	49
30	30	58	64
60	39	70	76
90	46	76	80
120	49	80	84
240	55	85	87

a) Mixed powders were allowed to stand in air for 170 h after shaking and then ESR spectra were recorded.
b) Silica-alumina calcined for 5 h at 200°C.
c) Silica-alumina calcined for 5 h at 400°C.
d) Silica-alumina calcined for 5 h at 600°C.

almost constant ($\sim 43 \times 10^{14}$ spins/g). The constant level for the binary powder system of PS and 1 wt % of SA_{200}, SA_{400}, or SA_{600} was attained at a shaking time of about 300, 240, or 240 minutes, respectively.

The increase in the number of radicals in the powder of PS alone with increase of shaking time is also shown in Table II. In this case, radicals were not observed at a small shaking time, but they appeared when the powder was vigorously stirred for a long period. This is probably because of the evolution of heat due to the mutual friction among PS particles. The increment of the number of spins in PS powder was found to increase with increase in the shaking time, although the number of radicals was always small.

Table II. The Effect of Shaking Duration on the Number of Spins/g in the Binary System of Potato Starch and Silica-alumina (1 wt %)[a]

Shaking duration (min)	Silica-alumina			
	None ($\times 10^{14}$ spins/g)	SA_{200}[b] ($\times 10^{14}$ spins/g)	SA_{400}[c] ($\times 10^{14}$ spins/g)	SA_{600}[d] ($\times 10^{14}$ spins/g)
5	<0.01	11	17	19
15	<0.01	24	28	30
30	0.01	30	34	35
60	0.02	33	36	37
90	0.03	37	40	41
120	0.06	39	42	42
240	0.13	41	43	43

a) Mixed powders were allowed to stand in air for 24 h after shaking and then ESR spectra were recorded.
b) Silica-alumina calcined for 5 h at 200°C.
c) Silica-alumina calcined for 5 h at 400°C.
d) Silica-alumina calcined for 5 h at 600°C.

Effect of Compressive Stress on the Number of Radicals

Binary System of Glycolic Acid and Silica-Alumina——Table III presents the effect of compressive stress on the number of radicals in the binary system of GA (10 wt %) and SA calcined at 200°C, 400°C, or 600°C. Inspection of Table III shows that the number of spins

increases with increase in the compressive stress and with increase in the calcination temperature of SA. However, the increase in the number of radicals gradually becomes smaller with increase in the compressive stress and finally the number of radicals tends to reach a plateau ($\sim 65 \times 10^{15}$ spins/g). A constant level for the binary powder of GA (10 wt %) and SA_{200} could not obtained in this experiment, but those for the binary powders of GA (10 wt %) with SA_{400} and SA_{600} were attained at compressive stresses of about 500 and 250 kg/cm^2, respectively.

Table III. The Effect of Compressive Stress on the Number of Spins/g in the Binary System of Glycolic Acid (10 wt %) and Silica-Alumina[a)]

Compressive stress (kg/cm^2)	Silica-alumina		
	SA_{200}[b)] ($\times 10^{15}$ spins/g)	SA_{400}[c)] ($\times 10^{15}$ spins/g)	SA_{600}[d)] ($\times 10^{15}$ spins/g)
1	21	42	49
10	27	46	55
50	36	55	58
100	43	59	61
250	49	62	64
500	56	65	64

a) The compressive stress was applied for 5 min after the mixed powder had been shaken for 15 min. After that, the powders were allowed to stand in air for 170 h and then ESR spectra were recorded.
b) Silica-alumina calcined for 5 h at 200°C.
c) Silica-alumina calcined for 5 h at 400°C.
d) Silica-alumina calcined for 5 h at 600°C.

Binary System of Potato Starch and Silica-Alumina——The effect of compressive stress on the number of radicals in the binary system of PS and 1 wt % of SA calcined at 200°C, 400°C, or 600°C is given in Table IV. It can be seen from Table IV that the number of spins increases with increase in the compressive stress and with increase in the calcination temperature of SA. In addition, the increase in the number of radicals is smaller with increase in the compressive stress and finally the number of radicals tends to approach asymptotically to a constant value ($\sim 43 \times 10^{14}$ spins/g). Constant values for the binary powder of PS and SA_{200} (1 wt %) could not obtained in our experiment, whereas those for the binary powders of PS with 1 wt % of SA_{400} and SA_{600} were attained at compressive stresses of about 500 and about 250 kg/cm^2, respectively.

As is also shown in Table IV, no radicals are observed in PS powder alone at a small compressive stress, but they appear when the powder is subjected to a large compressive stress. The increment of the number of spins in PS powder was found to increase with increase in the compressive stress, although the number of radicals was always small.

Effects of Other Mechanochemical Processes on the Number of Spins

Effect of the Particle Size of Silica-Alumina——Generally speaking, the number of radicals was found to increase with decrease in the size of SA particles. For example, the number of spins in the binary powder of GA (10 wt %) and SA_{400} having a particle size of 100—150, 150—200, or 200—250 mesh was determined to be 40, 42, or 46×10^{15} spins/g, respectively, at a constant shaking duration (15 min), and to be 52, 55, or 59×10^{15} spins/g, respectively, at a given compressive stress (50 kg/cm^2). In addition, the number of spins in the binary powder of PS and 1 wt % of SA_{400} possessing a particle size of 100—150, 150—200, or 200—250 mesh was found to be 27, 28, or 30×10^{14} spins/g, respectively, at a given shaking period (15 min), and to be 35, 36, or 38×10^{14} spins/g, respectiviely, at a definite compressive stress (50 kg/cm^2).

Table IV. The Effect of Compressive Stress on the Number of Spins/g in the Binary System of Potato Starch and Silica-Alumina (1 wt %)[a]

Compressive stress (kg/cm^2)	Silica-alumina			
	None ($\times 10^{14}$ spins/g)	SA_{200}[b] ($\times 10^{14}$ spins/g)	SA_{400}[c] ($\times 10^{14}$ spins/g)	SA_{600}[d] ($\times 10^{14}$ spins/g)
1	<0.01	24	28	30
10	0.01	27	32	33
50	0.02	33	36	37
100	0.08	35	39	40
250	0.21	39	42	43
500	0.39	41	43	43

a) The compressive stress was applied for 5 min after the mixed powder had been shaken for 15 min. After that, the powders were allowed to stand in air for 24 h and then ESR spectra were recorded.
b) Silica-alumina calcined for 5 h at 200°C.
c) Silica-alumina calcined for 5 h at 400°C.
d) Silica-alumina calcined for 5 h at 600°C.

Effect of Mixing Technique——The number of radicals was also found to depend on the mixing techniques, although quantitative results could not be obtained at the present stage. For instance, when the mixed powder of either GA and SA or PS and SA was ground for a certain period in an agate mortar, the number of spins was much greater than that generated in the same binary powder only shaken in a glass vessel for the same period. In addition, the number of spins showed a tendency to increase with increase in the intensity of grinding. Further, the number of radicals formed by shaking in a glass vessel was found to be a little less than that produced by shaking in a plastic vessel for the same duration.

Application to the Manufacture and Storage of Drugs

Though quantitative data are not available at the present stage, variation in the shape of the ESR spectrum and the production of light red color were observed in a binary powder of GA and SA on being allowed to stand, especially in a moisture-containing atmosphere, for a long period.[8] The intensity of this light red color increased with the progress of a reaction on the surface of SA. When the binary powder was transferred from a moisture-containing atmosphere to an atmosphere of dried air, however, the complexity of the ESR spectrum stopped increasing and the spectrum gradually changed to that observed for a mixture which had been allowed to stand in an atmosphere of dried air from the beginning. In addition, the intensity of the light red color of this binary powder practically stopped increasing. Therefore, the variation in the ESR spectrum and the production of the color were probably due to the reaction of GA with water on a solid acid site of SA. After reaction, the product molecule may be expelled from the acid site and then a fresh GA molecule may be newly adsorbed at the acid site, forming a radical. Further, the magnitude of the variation in the ESR spectrum and the intensity of this light red color in the binary powder of GA and SA allowed to stand in a moisture-containing atmosphere were also found to increase with increase in the shaking duration and with increase in the compressive stress. The initial application of a mechanical force to the powder presumably causes an increase in the number of radicals and then an increase in the rate of hydrolysis in a moisture-containing atmosphere. Therefore, radicals seem to be intermediates in the hydrolysis of GA. Next, the variation in the shape of the ESR spectrum was observed during the application of a mechanical force. A typical instance is provided by the ESR spectrum of the binary system of ascorbic acid and SA. In this case, as described in the previous paper,[8] the ESR spectrum of the mixture in an atmosphere of oxygen became very different from that in an atmosphere of nitrogen at one week after mixing. That is to say, when this binary powder was allowed to stand in an oxygen-containing atmosphere, the ESR spectrum changed

remarkably with time, probably due to the oxidation of ascorbic acid with oxygen. Both the number of radicals and the magnitude of this variation in spectral shape of the binary powder of ascorbic acid and SA were found to increase during the application of a mechanical force, such as shaking or compressing, in air, and increased with increase in the shaking duration and with increase in the compressive stress.

In general, the application of mechanical energy to a binary powder of SA and an organic compound affected, to varying degrees, both the mode of subsequent change in spectral shape and the number of spins both during and after the application of the mechanical force. Namely, the magnitude of the spectral variation upon application of a mechanical force seemed to correspond to the increase in the number of radicals. Therefore, one of the causes of chemical reactions, such as hydrolysis and oxidation, in these mixtures seems to be the formation of radicals on solid acids on the surface of SA.

Many important properties of drugs can be inferred from studies foreign to pharmaceutical sciences. In fact, the binary powders of GA and SA used in this work are not used as components of drugs; although PS is very frequently used in drugs, it is not mixed with SA in the manufacture of drugs. The binary systems of GA and SA and of PS and SA were adopted in this study only for experimental convenience. That is to say, the spectral intensity of the PS-containing binary powder was largest when PS was mixed with SA. As described in the previous paper,[8] the ESR spectrum of a binary powder of GA and SA gave a large spectral intensity and well-defined hyperfine splittings. Further, the intensity ratios of these hyperfine splittings of the adsorbed GA radical deviated markedly from integral values. In the future, the quantum chemical explanation of these intensity ratios will be of considerable interest, and time course studies of the shapes and intensities of these ESR spectra will be helpful for studies on the mechanisms of catalytic reactions over solid acids.

Among the aluminosilicates, powders of aluminum silicate and of magnesium aluminosilicate are actually used as components of drugs. From a mechanochemical point of view, results similar to those described above were also obtained in binary powders of general organic compounds and aluminosilicates. Furthermore, any physical and chemical changes in any materials, independent of whether aluminosilicate powder is present or not, seem to be accelerated by the application of mechanical energies. For example, radicals of PS produced by ultraviolet (UV) irradiation[11] disappeared gradually when the PS was mixed, for example, with salicylic acid, and the rate of disappearance of radicals was affected by mechanical processes such as shaking and compressing.

In conclusion, we should like to emphasize the importance of mechanochemical considerations in view of the modifications of the physical and chemical properties of powdery drugs that may occur in the manufacturing process. As described above, mechanical energies can induce chemical reactions during the manufacture of drugs and can also accelerate chemical reactions during the storage of drugs. The formation of radicals may be one of the main causes of chemical reactions in drugs. Actually, the physical and chemical properties of drugs also depend on the kinds of machines used in their processing, and are affected by operational techniques or conditions, even if the same machine is always used.

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9) Radicals once formed were found to be rather stable in water-free benzene solution. Therefore, DPPH

was dissolved in benzene, and mixed with SA or PS powder under stirring. After that, the benzene was removed under reduced pressure.

10) The number of spins in the binary powder of SA and DPPH decreased, though slowly, with the passage of time. Therefore, the value was estimated by extrapolation of the numbers of spins from 0.5 to 24 h after mixing to that immediately after mixing.

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