dehyde oxime.

(2) By the action of hydroxylamine and sodium acetate mixture, (II) formed *o*-formamidobenzaldehyde oxime.

(3) Quinazoline 3-oxide was obtained by terating (I) or (II) with acetone or *p*-nitrobenzaldehyde, by formylation of *o*-aminobenzaldehyde oxime with formic acid or ethyl orthoformat, and by dehydration of *o*-formylaminobenzaldehyde oxime with conc. sulfuric acid.

(4) (I) behaved like (II) toward ferric chloride, acetone, and sodium hydroxide and was proved to be a molecular compound of quinazoline 3-oxide and (II).

Also, based on the chemical structure of the intermediates, the mechanism of the specific hydroxylamine reaction shown in Chart 3 is proposed.

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## 90. **Jun Hasegawa**: Studies on Tablets. IV.[1] Frictional Electrification of Crystalline Medicines.

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It is a well known phenomenon that in two insulators like silk, glass, fur, or ebonite, when rubbed with each other and separated, a static charge of opposite signs is produced on their surface. With recent advances in industrial processes several undesirable side effects due to static charge such as adhesion of small dust particles to synthetic fibers became evident.

The effect of this phenomenon is also found in the fields of pharmacy. When crystalline Aspirin is crushed and mixed in a mortar, the powder adheres so firmly to the surface of the tools employed that its removal is very difficult. When medicines are sieved or filled in bottles by automatic machines, adhesion of crystals to wire nets, container surfaces, or to each other may be so great as to hinder or even make it impossible to complete the process. When crystals of Aspirin are washed with benzene after acetylation in the course of manufacture, static charges from friction appear between the crystals and the container.

Depending upon the amount, the electrical capacity of apparatus, and the electrical resistance to leakage, thousands of volts may be formed and becomes a dangerous fire hazard.[2]

Dry crystals may adhere to the glass wall of ampules giving an erronous impression of wetness. The effect of static electricity may also be observed in tablet manufacture.

In spite of the many side effects of static electricity, as described above, very few reports on the phenomenon have been presented. It is the purpose of this study to present model experiments on frictional electrification of crystalline medicine and to discuss preventive measures against formation of static charges when handling powders.

The author wishes to express his gratitude to Prof. H. Nogami of this University for his kind guidance and encouragement and to Prof. Y. Suge and Dr. Z. Otaki, Laboratory of Applied Physics, University of Tokyo, for their helpful suggestions and technical guidance throughout this study.

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* Hongo, Tokyo (長谷川 淳).

1) Part III: This Bulletin, **5**, 15(1957).

2) N. Makino, *et al.*: Bull. Electro-Technical Lab., **16**, 273.

## Experimental

1) **Material**—Materials used were medicinals of J. P. VI grade and special purification process was not employed, since the differences of static electrification between brands and lots of Aspirin crystals could not be recognized.

Material was frictionated by the cleaned standard sieve, weighed, wrapped in paraffine paper, kept in calcium chloride desiccator in vacuum, and used for the experiment.

2) **Vacuum Tube Voltmeter**—The circuit diagram[3] is given in Fig. 1, in which a low plate voltage

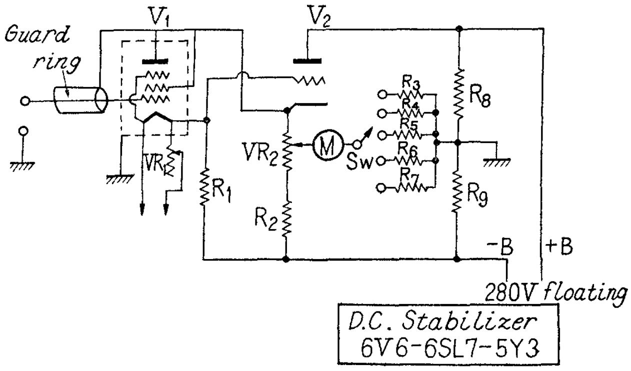


Fig. 1. Circuit Diagram of Vacuum Tube Voltmeter

| | | | |
|---|---|---|---|
| $R_1$ | 15 MΩ ¼ W | $R_9$, $R_{10}$ | 20 KΩ 2 W |
| $R_2$ | 200 KΩ ½ W | $VR_1$ | 100 Ω |
| $R_3$ | 50 KΩ ¼ W, 1% | $VR_2$ | 50 KΩ |
| $R_4$ | 100 KΩ 〃 | $V_1$ | 3 S 4 |
| $R_5$ | 500 KΩ 〃 | $V_2$ | ½ 12 AU 7 |
| $R^6$ | 1 MΩ 〃 | M | ± 50 μA |
| $R_7$ | 2 MΩ 〃 | | |

(about 7.5 V) is supplied to 3S4 ($V_1$) and a cathode follower circuit is used for wide linearity. The bottom of $V_1$ was treated with silicone varnish KR 223 (Shin-etsu Chem. Co.) and heated to about 150° for 24 hr. to secure good insulation. $V_1$ was kept in a copper-shielded box with a drying agent to reduce outer leakage. Sensisivity of the instrument was controlled by adjusting Sw from ±5 to 100 V.

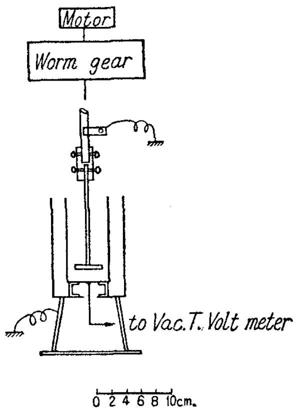


Fig. 3. Apparatus for Agitation of Crystals

3) **Determination of Charge**—Charged crystals were placed in the Faraday cylinder shown in Fig. 3, in which the capacity was adjusted from 40 to 254 pF by connecting the parallel condenser. The induced voltage was determined and the charge was calculated from the values of voltage and capacity in $10^{-10}$ coulomb throughout this work. The calibration of the vacuum tube voltmeter was carried out by giving known voltages to the Faraday cylinder.

4) **Procedure of Frictional Electrification**—Copper, brass, glass, and paraffin paper were formed into a flat-bottomed chute of 5×35×1 cm. in size. These materials were considered to be frequently in contact with crystals when sieving or storing medicines. The crystals to be tested were scattered evenly on an area of 5×10 cm. at a distance of 5 cm. from one side of the chute. Histeresis of crystals on static electrification was reduced by the irradiation of β-ray for 60 sec. with 1 mc of $^{204}$Tl. The chute was inclined slowly, transferring the crystals into the Faraday cylinder and the charge was determined as described above.

5) **Climatic Conditions**—The experiment was carried out at 14~24° and relative humidity of 48~63%, since the frictional electrification may be affected by climatic conditions.

6) **Experimental Design and Level of Factorial**—The following levels were selected for factorials.

i) Crystals: Three derivatives of salicylic acid were used. $C_1$=Aspirin, $C_2$=salicylamide, and $C_3$=phenyl salicylate.

ii) Particle size of crystal: $P_1$=20/32, $P_2$=32/42, and $P_3$=42/60 mesh.

3) Z. Otaki: J. Appl. Phys. Japan, **24**, 339(1955).

iii) Weight of crystal : $W_1=0.5$, $W_2=1.0$, $W_3=1.5$ g.

iv) Material of chute : a) The effect of grounding was examined by comparing the results when the metal chute was electrically floated with polystyrol resin and grounded. b) Frictional electrification was determined using electrically floated chutes of copper, brass, glass, and paraffin paper. These factorials were combined, repeating twice, and $3\times3\times3\times4\times2$ determinations were carried out in a randomized block design.

7) **Treatment of Crystal with Surfactant**—(Expt. 4) : Each of Tween 40, stearic acid, and sodium laurylsulfate was dissolved in 60% acetone to make 0.5% solution and 1.0 g. of surfactant solution was sprayd on 20 g. of crystal, dried in $CaCl_2$ desiccator in vacuum. Frictional electrification was determined as in Expt. 1 and compared with the result obtained by treating with 60% acetone in the same manner.

## Results and Discussion

The result of Experiment 1 is given in Table I, in which the value given is the mean of two determinations. The analysis was carried out as follows : The factorial

Table I. Frictional Electrification of Crystals

| | Part. size | Wt. (g.) | Copper | Copper E | Brass | Brass E | Glass | Paraffin paper |
|---|---|---|---|---|---|---|---|---|
| Aspirin | 20/32 | 0.5 | 9.5 | 11.7 | 12.1 | 14.6 | 9.7 | 19.6 |
| | | 1.0 | 25.4 | 26.8 | 26.8 | 25.0 | 22.3 | 36.5 |
| | | 1.5 | 38.0 | 36.5 | 38.8 | 38.4 | 28.1 | 46.8 |
| | 32/42 | 0.5 | 21.6 | 19.2 | 19.0 | 21.5 | 11.0 | 28.8 |
| | | 1.0 | 32.1 | 32.5 | 30.8 | 27.7 | 22.3 | 45.6 |
| | | 1.5 | 43.8 | 45.8 | 46.4 | 45.3 | 33.3 | 70.6 |
| | 42/60 | 0.5 | 24.7 | 26.3 | 25.1 | 25.8 | 13.1 | 44.9 |
| | | 1.0 | 45.1 | 47.3 | 44,3 | 46.0 | 26.6 | 88.4 |
| | | 1.5 | 68.0 | 70.0 | 67.2 | 62.9 | 39.4 | 116 |
| Salicylamide | 20/32 | 0.5 | 4.6 | 4.4 | 3.8 | 4.1 | 3.9 | 9.8 |
| | | 1.0 | 10.6 | 9.9 | 7.7 | 8.4 | 10.2 | 15.6 |
| | | 1.5 | 17.1 | 18.0 | 12.6 | 9.9 | 15.8 | 25.7 |
| | 32/42 | 0.5 | 9.5 | 9.0 | 7.7 | 7.1 | 6.7 | 22.3 |
| | | 1.0 | 21.3 | 22.2 | 15.2 | 14.5 | 16.1 | 50.4 |
| | | 1.5 | 28.5 | 27.4 | 22.9 | 22.5 | 22.0 | 79.5 |
| | 42/60 | 0.5 | 19.8 | 22.4 | 12.0 | 10.2 | 17.4 | 44.2 |
| | | 1.0 | 36.9 | 37.3 | 24.1 | 18.7 | 33.4 | 90.6 |
| | | 1.5 | 54.4 | 56.1 | 32.8 | 32.1 | 48.4 | 12.8 |
| Phenyl salicylate | 20/32 | 0.5 | 2.3 | 2.5 | 1.9 | 2.6 | 3.4 | 11.7 |
| | | 1.0 | 4.1 | 4.2 | 4.9 | 4.9 | 6.1 | 22.7 |
| | | 1.5 | 6.7 | 6.4 | 6.8 | 7.0 | 10.1 | 36.5 |
| | 32/42 | 0.5 | 2.7 | 2.4 | 3.0 | 3.0 | 4.5 | 11.1 |
| | | 1.0 | 5.6 | 6.1 | 5.4 | 6.7 | 9.3 | 24.2 |
| | | 1.5 | 7.9 | 7.6 | 7.8 | 7.9 | 16.1 | 37.1 |
| | 42/60 | 0.5 | 2.7 | 3.5 | 3.0 | 3.0 | 5.8 | 15.1 |
| | | 1.0 | 6.9 | 6.0 | 6.3 | 6.3 | 14.0 | 29.6 |
| | | 1.5 | 9.5 | 8.7 | 7.5 | 8.0 | 19.0 | 40.4 |

Each value shows a negative charge, in $10^{-10}$ coulomb.

analysis of the result is shown in Table II A, in which the effect of grouding was examined and the pooled higher interactions were used for the error term at the significant test. As shown in Table II A, the main effect and interaction of grounding were not significant at 5% level. Therefore, the effect of grounding was not recognized.

The effect of factorials was examined on electrically floated chutes, as shown in Table II B, and each of the main effect and interaction was highly significant, as shown in Figs. 2A and 2B. From these results, it may be concluded as follows : i) The static charge increases with the increase of frictional surface area since the main effect of P and W is highly significant. ii) The effective surface area of friction may be spcifically different for each crystal, because the interactions of $C\times W$, $C\times P$, and $W\times P$ are highly significant. iii) The free rotation of particles was not observed during transfer

TABLE II. Analysis of Variance

| Factor | A φ | A M.S. | B φ | B M.S. |
|---|---|---|---|---|
| Main effect: | | | | |
| R (replacement) | 1 | 10.5 | 1 | 0.65 |
| C (crystal) | 2 | 15468.2 ** | 2 | 11825.3 ** |
| W (weight) | 2 | 5938.8 ** | 2 | 10409.8 ** |
| P (particle size) | 2 | 3708.2 ** | 2 | 7680.0 ** |
| M (chute) | 1 | 445.8 ** | 3 | 8730.3 ** |
| E (earth) | 1 | 0.52 | | |
| Interaction: | | | | |
| C×W | 4 | 1044.5 ** | 4 | 769.1 ** |
| C×M | 2 | 349.4 ** | 6 | 557.2 ** |
| C×P | 4 | 762.6 ** | 4 | 1453.1 ** |
| W×M | 2 | 50.5 ** | 6 | 611.9 ** |
| W×P | 4 | 215.4 ** | 4 | 484.3 ** |
| M×P | 2 | 153.3 ** | 6 | 904.7 ** |
| C×E | 2 | 1.34 | | |
| R×E | 1 | 1.61 | | |
| W×E | 2 | 5.13 | | |
| M×E | 1 | 5.89 | | |
| Error | 181 | 8.546 | 175 | 75.61 |

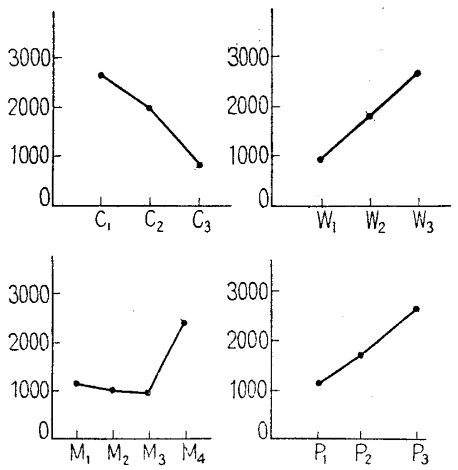


Fig. 2. (A) Main Effect

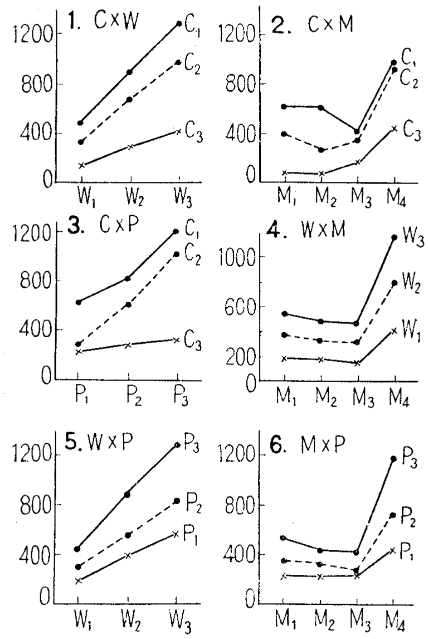


Fig. 2. (B) Interactions

of phenyl salicylate into the Faraday cylinder. It may have been caused by its tendency to stick, which is understandable as the interaction of C×P. iv) From the highly significant effect of C, M, C×M, W×M, and M×P, it may be considered that the frictional electrification of crystals is specifically determined by the combination of crystal, substance in contact, crystal form, and degree of free rotation of particle, etc. v) The charge was negative within the range of the experiment and it might be related with the electrical properties of the crystal since they were derivatives of salicylic acid.

The frictional electrification was determined on some inorganic and organic medicines using these chutes in Expt. 2 in which, since it was difficult to use the sample of same particle size, a suitable fraction of crystalline medicines was used. The results are given as the mean value of two determinations. It may be concluded as follows:

i) The frictional electrification was very high in the case of $HgCl_2$ and nearly the same with barbital, but not with NaCl or KCl, and relatively small charges were found with urea or hexamine, while very large charges were determined with barbital or sulfadiazine. Such large difference may not be found between organic and inorganic medicines. The direct relationship between amount of charge and water solubility could not be determined. It is supposed that water solubility may have an effect on leakage of the charge. ii) Positive charges were found in some combinations, shown in Table III,

TABLE III. Frictional Electrification of Crystals

| | Particle size* | Copper | Brass | Glass | Paraffin paper |
|---|---|---|---|---|---|
| NaCl | c | − 7.0 | − 8.5 | − 7.6 | − 5.9 |
| KCl | c | − 2.0 | + 6.5 | − 3.1 | − 2.7 |
| $KClO_4$ | a | − 0.34 | + 5.4 | + 0.66 | + 6.84 |
| $HgCl_2$ | a | −21.2 | −21.6 | −24.4 | −41.0 |
| Talc | | − 9.2 | −11.3 | −11.3 | − 5.2 |
| $H_3BO_3$ | b | − 8.0 | − 7.7 | − 3.6 | − 8.8 |
| Acetanilide | b | ∓** | ∓ | ∓ | ∓ |
| Acetophenetidine | a | ∓ | ∓ | ∓ | −28.6 |
| Benzoic acid | b | − 3.2 | ∓ | ∓ | −15.7 |
| Ethyl *p*-aminobenzoate | c | −18.1 | − 8.4 | −29.0 | −34.0 |
| Barbital | c | −37.6 | −32.1 | −28.9 | −50.4 |
| Sulfathiazole | a | −12.2 | −11.1 | − 6.2 | −26.2 |
| Sulfadiazine | b | −31.8 | −23.6 | −15.9 | −35.0 |
| Urea | a | − 0.05 | − 0.4 | −10.9 | + 1.9 |
| Camphor | a | + 4.1 | + 6.4 | + 4.5 | − 2.8 |
| Hexamine | a | + 1.8 | + 4.5 | + 4.8 | + 3.7 |
| Aminopyrine | a | +16.7 | +15.1 | +13.8 | + 5.9 |

* a=20/32 mesh, b=32/42 mesh, c=42/60 mesh

** A negative charge was found at first and a positive one appeared.

Each value is given in $10^{-10}$ coulomb/1.0 g.

especially with hexamine and aminopyrine in all cases, though only negative charges were found in Expt. 1. It is considered that adsorbed water may have an effect on the developing mechanism of static charges. The true mechanism, however, may not be so simple, since it was positive with camphor and negative with sulfa drugs or ethyl *p*-aminobenzoate that have a free amino group. Therefore, the sign and the amount of charge may be related to the combination of physical and chemical properties of crystals or substances in contact. iii) Acetanilide, acetophenetine, and benzoic acid behaved quite differently from other crystals, showing negative charges at first and then positive. This is represented by the sign of ∓ in the table. Adhesion of crystals to the chute was observed. The same phenomenon as described above was found by Gill[5] who showed that a positive charge and then a negative charge was produced on an insulated metal plate by the free fall of sand on it. Suge and Otaki[6] found the same inversion of charge with powdered synthetic polymers and concluded that it may have been caused by the effect of self-electric field.

The inversion of charges was studied in Expt. 3 in which 20 g. of crystals was placed in the Faraday cylinder as shown in Fig. 3, agitated with the grounded brass or T-shaped glass rod at the rate of 30 r.p.m., and changes in induced voltages were observed continuously.

The reproducibility of the experiment was not satisfactory since the adhering crystals sometimes fell down by mechanical shock. Typical results are given in Figs. 4 and 5 in which A is the group of acetanilide, acetophenetidine, and benzoic acid that

5) E.W.B. Gill: Nature, **162**, 568(1949).
6) Y. Suge, Z. Otaki: A lecture presented at the Annual Meeting of the Society of Applied Physics of Japan, April 3, 1957.

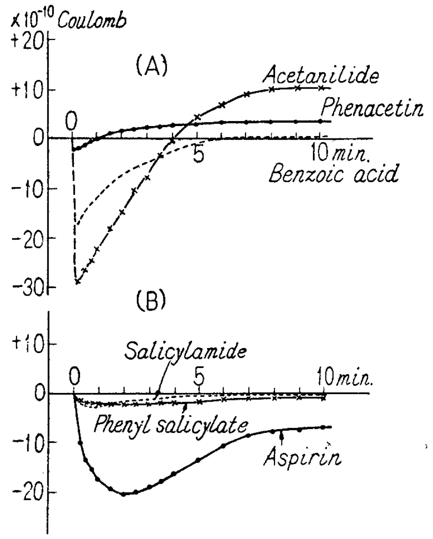


Fig. 4. Frictional Electrification, agitated with a Brass Rod

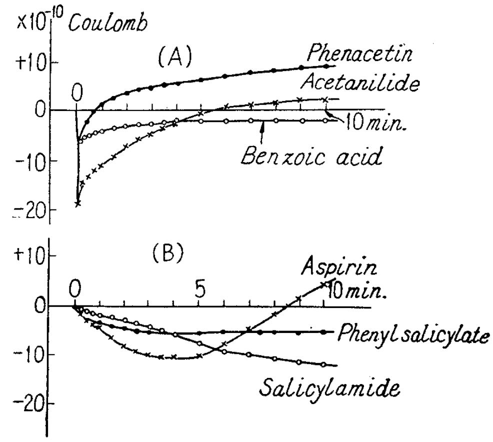


Fig. 5. Frictional Electrification, agitated with a Glass Rod

behaved differently in the chute experiment and B is the group consisting of Aspirin, salicylamide, and phenyl salicylate.

In these figures, the difference in frictional electricity between the two groups was obtained at the initial stage. The maximum negative charge was found within 15 sec., decreased gradually by the formation of opposite charges, and reached an equilibrium within 7∼8 min. with group A. With group B, however, the maximum negative charge was determined very slowly, after 30 sec. or about 4 min., then lessened, and reached equilibrium. It was observed with the naked eye that the adhesion of crystals to the surface in contact affected the inversion of charge sign in the chute experiment. A marked tendency of crystals to stick to the agitator was also found in group A in this experiment. Therefore, it may be concluded that the different behavior of the crystals of group A is due to the marked adhesion of the crystals. It is not clear which properties affected the adhesion, but it may partly be due to compression and is interesting since nearly the same static charge obtained in the chute experiment was found in the tablet formation experiment, as will be described in a later report. It is considered that the adhesion may not be caused by a simple static-electric force but also by same kind of a bond like Van der Waals' force. Harper described in his report[7] that the maximum distance which electrons could transfer from one face to another was estimated to be about 25 Å and it might be several Å with atomic ions. Under such conditions Van der Waals' force may be relate to adhesion. At any rate, if a crystal adheres by a mechanism, then the direction and the degree of movement of charged particle may result in the development of an opposite charge. Moreover, the adhesion of crystal is not limited to one layer, so that the result will be complex.

The effect of surfactant on frictional electrification was examined in Expt. 4. It may be possible to reduce the development of static charge since the surfactant film formed on the crystal surface increases electrical leakage. The result carried out in a randomized block design is given in Table IV as a mean value of two determinations. From the results, the effect of surfactant is considered as very specific, i.e. the marked reduction of the phenomenon to 1% was observed in the chutes with paraffin paper but not with other metal chutes and about 1/2 to 1/3 of opposite charge was determined even

7) W. R. Harper: Proc. Roy. Soc., A, **205**, 83(1951).

Table IV. Effect of Surfactants

| | * | Copper | Brass | Glass | P. paper |
|---|---|---|---|---|---|
| Aspirin, 32/42 mesh, 1.0 g. | Control | −30.5 | −31.6 | −25.2 | −41.7 |
| | Sod. laur. sulf. | + 4.5 | +14.0 | + 6.8 | − 3.3 |
| | Tween 40 | + 9.9 | +12.5 | +13.3 | − 0.5 |
| | Stearic acid | − 6.5 | − 2.8 | − 3.4 | −23.4 |
| Salicylamide, 32/42 mesh, 1.0 g | Control | −22.5 | −17.1 | −15.7 | −46.5 |
| | Sod. laur. sulf. | +14.1 | +16.3 | +13.0 | − 3.2 |
| | Tween 40 | + 4.7 | + 7.7 | +12.8 | − 3.7 |
| | Stearic acid | − 7.9 | − 4.0 | − 7.0 | −32.4 |

* 1.0 g. of 5% solution in 60% acetone was sprayed on 20 g. crystal.
Each value is given in $10^{-10}$ coulomb.

with the same combination of Aspirin–Tween 40. The same tendency was found with salicylamide. The effect with sodium laurylsulfate was quite the same as the one with Tween 40. The inversion of charge was not observed with stearic acid, but the effect was remarkable with metal or glass chute and not with paraffin paper chute.

## Summary

The frictional electrification of 6 inorganic and 13 organic medicinal crystals was examined.

The crystal was slid down on flat-bottomed chute into a Faraday cylinder and the induced voltage was determined by a vacuum tube voltmeter with a very small leakage of $10^{-13}$ to $10^{-14}$ A. The prediction of the phenomenon was very difficult since the sign and the amount of charge was determined by the experimental conditions, but the following tendencies were found.

1) The charge found at the chute made of paraffin paper was larger than the one made of metal or glass. The grounding of the metal chute was not effective on avoiding frictional electrification.

2) A relatively small charge was found with water-soluble crystals and a larger one with water-insoluble crystals.

3) Acetanilide, acetophenetidine, and benzoic acid behaved quite differently, i.e. negative charges and then positive charges were found on the crystals in the chute experiment. It was evidenced that this was caused by the adhesion of crystal.

4) In the treatment of crystals with surfactant, the development of charge was reduced to about 1/100 with the combination of Aspirin–Tween 40–paraffin paper chute, but an opposite charges was observed in some cases.

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