Hydrogen Fluoride Adduct Formation of Medicinal Compounds and Its Application to Particle Size Reduction

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It was confirmed that griseofulvin, sulfanilamide and theophylline form HF adducts with combining ratios of 1:1 (griseofulvin:HF), 1:2 (sulfanilamide:HF) and 1:3 and 1:2 (theophylline:HF). The thermal and other physico-chemical properties of these adducts and the recovered medicinals were investigated by differential scanning calorimetry, thermogravimetry, X-ray powder diffractometry, infrared spectroscopy and microscopy. Effective particle size reduction was achieved by desorbing HF from the adducts.

Keywords—griseofulvin; sulfanilamide; theophylline; hydrogen fluoride adduct; hydrogen chloride salt; hydrogen fluoride adduct thermal behavior; hydrogen fluoride adduct physico-chemical property; hydrogen fluoride sorption; hydrogen fluoride desorption; particle size reduction

In a series of studies, the authors have reported a method of particle size reduction by making use of the phase conversion from a solvate or adduct to the original medicinal compound. In the present study, adduct formation was attempted between anhydrous HF, which is known to be one of the most acidic substances, and four medicinal compounds (griseofulvin, sulfanilamide, theophylline and phenacemide). Thermal and other physico-chemical properties of the HF adducts and the recovered medicinals were investigated by differential scanning calorimetry, thermogravimetry, X-ray powder diffractometry, infrared spectroscopy and microscopy. The HCl salt of sulfanilamide was prepared and its properties were determined for reference.

Experimental

Materials—Griseofulvin: Recrystallized from acetone.
Sulfanilamide: Needle crystals (polymorphic z form) recrystallized from n-butyl alcohol were used.
Theophylline: The anhydrous form was used. Monohydrate crystallized from water was dried at 100 °C for several hours before use.
Phenacemide: Commercial product was used without further purification.
Anhydrous Hydrogen Fluoride: Commercially available liquid HF in a steel bomb (Daikin Kogyo Co., Ltd.) was used. The guaranteed purity was over 99.99%.
Hydrogen Chloride: Commercially available liquid HCl in a steel bomb (Tsurumi Soda Co., Ltd.) was used without further purification. The guaranteed purity was over 99.7%.

Preparation of HF Adducts—An HF-reaction apparatus type I provided by Peptide Institute, Inc. was used. The apparatus, made of polychlorotrifluoroethylene, was evacuated first, then a vessel (inert to HF) containing the sample material was cooled with an acetone-dry ice bath. When anhydrous HF gas was introduced gradually into the vessel by single step distillation, it was liquefied and dissolved the sample material. After several minutes, the acetone-dry ice bath was removed from the vessel. The apparatus was connected to an HF vacuum line equipped with an absorption cylinder (CaO) and the excess of HF in the vessel was allowed to evaporate through the vacuum line. Several hours of additional evacuation were done from the point where almost all the liquid HF had been eliminated. Thereafter, samples were stored in tight containers, if necessary in a refrigerator.
Preparation of Sulfanilamide HCl Salt — When dried HCl gas was introduced gradually into an ethyl alcohol solution of sulfanilamide in a flask at room temperature, immediate crystallization occurred. Small needle-like transparent crystals were obtained by filtration.

Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG) — Simultaneous measurements of DSC and TG were done by using a Thermoflex TG-DSC (Rigaku Denki Co., Ltd.) under a nitrogen gas flow of 50 ml/min. Eliminated HF gas was trapped at the gas outlet. For the measurements under closed conditions, an SSC/580-DSC 20 differential scanning calorimeter (Seiko Instruments & Electronics) was used, and each sample was sealed into a container capable of withstanding a pressure of about 50 atm.

X-Ray Powder Diffractometry — The instrument used was a JEOL JDX-7F X-ray diffractometer (Cu-Kα radiation, λ = 1.542 Å, Ni filter).

Infrared (IR) Spectroscopy — IR spectra (Nujol mull method) were measured with a Jasco IRA-1 grating infrared spectrophotometer.

Microscopic Observation — An FHF-Tr-IV microscope (Olympus Optical Co., Ltd.) was used. For hot-stage microscopy, an FP 52 micro-furnace (Mettler) was installed on the microscope.

Scanning Electron Microscopy (SEM) — An MSM-4 scanning electron microscope (Hitachi-Akashi) was used.

Results and Discussion

HF Adduct of Griseofulvin

Anhydrous HF solution of griseofulvin showed a reddish yellow tinge, and was evaporated to yield yellow crystals. This coloration phenomenon may be ascribed to molecular interaction of griseofulvin with HF. The crystals, however, turned white gradually during the process of HF evacuation. In the present study, we used the white crystals obtained by additional evacuation (ca. 1 h).

Determination of the Combining Ratio and X-Ray Diffractometry — The TG curve of the white crystals from HF solution showed a gradual weight decrease immediately after the measurement run and the weight loss (attributable to HF dissociation) continued until about 170 °C. From 6 measurements, the value of the combining ratio was within the range of 1:1.0-1.3 mol (Fig. 1(c)). When sample crystals were held at room temperature (24 ± 1 °C) under open conditions, HF dissociation proceeded gradually and the composition changed to 1:0.8-1.0 mol after a few hours. As is shown in Fig. 2, the powder X-ray diffraction pattern of the sample material was completely different from that of griseofulvin itself, which

![Fig. 1. DSC and TG Curves of Griseofulvin and Its 1:1 HF Adduct](image)

(a), DSC curve of griseofulvin under semiclosed conditions: sample weight, 7.99 mg; heating rate, 5 °C/min. (b) and (c), DSC and TG curves of 1:1 HF adduct under open conditions: sample weight, 13.93 mg; heating rate, 10 °C/min. (d), DSC curve of 1:1 HF adduct under closed conditions: sample weight, 6.15 mg; heating rate, 2 °C/min.

![Fig. 2. X-Ray Diffraction Patterns of Griseofulvin and Its 1:1 HF Adduct (2θ scan speed: 4°/min)](image)

(a), griseofulvin; (b), 1:1 HF adduct.
indicates the formation of an HF adduct possessing an intrinsic crystal structure. No difference was found between the diffraction pattern of the HF adduct possessing a stoichiometric combining ratio of 1:1 and that of a sample having more HF, such as 1:1.3. On the basis of these results, we may conclude that the HF adduct formation of griseofulvin occurs at least with equimolar ratio (1:1). Combining of excessive HF may be caused by adhesion on the surface or to small cavities of the sample material.

**Thermal Behavior**——When DSC measurement of the HF adduct was done under open conditions, the DSC curve showed three endothermic peaks and an exothermic peak, as depicted in Fig. 1(b). Since the last endothermic peak at about 220 °C is due to the melting of griseofulvin, the first shallow endothermic peak from 60 to 140 °C and the exothermic peak at about 150 °C may be attributable to dissociation of HF and retarded crystallization of recovered griseofulvin, respectively. An endothermic peak at about 160 °C may suggest the possibility of existence of a lower adduct.

On the other hand, when DSC was done under closed conditions (Fig. 1(d)), a sharp endothermic peak with a shoulder appeared at about 120—140 °C and no heat effect occurred below this temperature. Since the sample can be treated as a condensed system under such conditions, this peak would be attributable to peritectic transition of the HF adduct. Successive broad endothermic heat effects at about 150—190 °C must reflect fusion of griseofulvin in the presence of the liquid derived from the adduct.

**IR Spectra**——The IR spectra of griseofulvin and its HF adduct are depicted in Fig. 3. The HF adduct showed a new absorption band in the wide range of 3680—3060 cm\(^{-1}\). The absorption band of griseofulvin at 1715 cm\(^{-1}\), which is attributable to the C=O group in the benzofuran ring (3-ketone stretching band), showed a slight downward frequency shift (ca. 5 cm\(^{-1}\)) and was less intense after HF adduct formation. At the same time, the 4'-ketone stretching band (in the cyclohexene ring) of griseofulvin at 1665 cm\(^{-1}\) was broadened and extended toward the higher frequency region by about 15 cm\(^{-1}\). Changes in the IR spectrum in the finger-print region on HF adduct formation are very similar to those of the chloroform solvate.\(^{2}\) From this spectral evidence, it is supposed that HF adduct formation can be ascribed to hydrogen bonding between griseofulvin and HF.

**HF Adduct of Sulfanilamide**

When crystals of sulfanilamide were dissolved in HF solution and excess HF was eliminated, crystallization did not occur immediately. After standing at room temperature for a few days, gradual solidification proceeded and a white material was obtained.

**Determination of the Combining Ratio and Thermal Behavior**——From four TG measurements, the combining ratio of HF was determined to be 1 : 2.00 ± 0.01 (sulfanilamide : HF), as shown in Fig. 4(c). In DSC measurements under closed conditions, only a sharp endothermic peak appeared at about 142 °C (curve (h)). On the other hand, under open conditions, three to
four endothermic heat effects were exhibited in the DSC curve. The first broad endotherm, accompanied with a gradual weight decrease, began at about 50–60 °C and the HF elimination proceeded till the appearance of the second endothermic peak. At the temperature of the sharp endothermic peak (132 °C), complete dissociation of HF occurred (curves (c) and (e)). Depending on the magnitude of the HF dissociation below 132 °C, the DSC patterns varied considerably as shown in Fig. 4(b), (d) and (f). In the DSC curve (b) measured at a heating rate of 5 °C/min, the HF content was about 0.8 mol at that temperature, and a successive endothermic peak appeared at 141 °C (peak maximum). The slower the heating rate, the smaller the endothermic peak, and it finally disappeared when complete elimination had occurred prior to that temperature. The highest endothermic peak at 164 °C is due to melting of recovered sulfanilamide.

On the basis of these results, the following conclusions can be drawn.
1. Sulfanilamide forms an HF adduct with a molar ratio of 1:2 (sulfanilamide:HF), and the HF adduct has a congruent melting point at 142°C.

2. Sulfanilamide and the HF adduct show a eutectic temperature of 132°C, below which temperature HF dissociation from the adduct proceeds as a solid-gas phase reaction.

**IR Spectra** — In the IR spectrum of the HF adduct (Fig. 5(b)), a characteristic broad absorption band appeared at about 2180—1900 cm⁻¹. Absorption spread to the region of 1900—1540 cm⁻¹ on adduct formation, instead of two sharp absorption bands at 1635 and 1595 cm⁻¹ (attributable to NH deformation) in the spectrum of sulfanilamide (curve (a)). Further, a new absorption band appeared between 1280 and 1230 cm⁻¹. These absorption bands caused by HF adduct formation were not recognized in the spectrum of the HCl salt of sulfanilamide, as is depicted later (Fig. 7). In the NH stretching frequency region, three absorption bands appeared between 3400 and 3040 cm⁻¹ (curve (b)). Although the number and position of absorptions in this region for sulfanilamide are affected somewhat by the various physical forms, each of the polymorphic α, γ and δ forms shows four bands (the higher two are attributed to vNH and the lower two to vsO₂N⁺), the β form shows three and the monohydrate five within 3600—3100 cm⁻¹. The spectrum of the HF adduct exhibited strong downward shifts of the vNH bands or disappearance of one or two of the bands. These IR data suggest that dipole-induced dipole interaction or hydrogen bonding between sulfanilamide and HF plays a major role in the adduct formation.

**HCl Salt of Sulfanilamide**

Simultaneous TG-DSC curves of the HCl salt of sulfanilamide are shown in Fig. 6(a) and (b). A broad endothermic peak appeared between 150 and 200°C which corresponds to a weight decrease of 1 mol of HCl. A small endothermic peak that appeared at about 160°C is attributable to the melting of sulfanilamide recovered partially by dissociation of HCl on heating. It can be said that the HCl salt of sulfanilamide melts at a higher temperature than the original sulfonamide, accompanied with decomposition of the HCl salt. This conclusion was supported by visual observation by hot-stage microscopy.

In the IR spectrum of the HCl salt, the NH deformation bands near 1600 cm⁻¹ were extremely weak (Fig. 7).

**HF Adducts of Theophylline**

**Determination of the Combining Ratio and Thermal Behavior** — Sample material obtained from an anhydrous HF solution of theophylline was confirmed to exist as a 1:3 HF adduct (theophylline:Hf = 1:2.9 ± 0.2) by simultaneous TG-DSC measurements under open conditions (Fig. 8(c) and (d)) and direct weighing of the sample before and after measurement by using a semimicrobalance. The DSC curve of the 1:3 adduct showed an endothermic heat effect between 40 and 75°C, and the TG curve indicated a first step of weight decrease corresponding to 1 mol of HF. Then HF dissociation proceeded up to about 180—200°C. The recovery of theophylline was proved by the appearance of the highest endothermic DSC peak at 270°C (melting of theophylline). This thermal behavior suggests the formation of a lower 1:2 adduct during heating. Incidentally, the DSC curve exhibited unusual heat effects, some abrupt endothermic peaks that might be attributable to the escape of dissociated HF molecules entrapped in the solid phase, between 70 and 150°C in the process of HF dissociation from the 1:2 adduct. On hot-stage microscopy, however, no change of appearance was noticed in the adduct crystals during heating in the temperature range of this complicated heat effect. It was indicated that the particle size of the HF adduct influences the DSC patterns. In the case of a sample composed of finer particles (curve (e)), the first endothermic heat effect became smaller, another broad endotherm followed by an exotherm appeared at about 100°C, and no abrupt irregular endothermic heat effect was shown. Therefore, it is supposed that the composition of the 1:3 adduct is easily changed merely by
trituration, and the broad endothermic and successive exothermic peaks may be ascribed to dissociation of the 1:2 adduct to HF-free theophylline and retarded crystallization, respectively.
When DSC measurement of the 1:3 adduct was done under closed conditions, as is shown by curve (f), the first sharp endothermic peak with a shoulder appeared at about 70 °C, and an endothermic peak and a rather flat exothermic peak followed between 90 and 210 °C. In the closed heating system, evaporation of HF was restricted inside the container, unless the container was ruptured by the pressure increase; therefore, the change in the sample composition would be small. The endothermic peak at about 70 °C is probably attributable to liquefaction caused by a peritectic or eutectic phase reaction, while the shoulder peak at about 85 °C should represent melting either of HF-free theophylline or of the HF adduct. The appearance of the following endothermic peak suggests the partial formation of the 1:2 adduct under the conditions adopted.

**X-Ray Diffractometry**—The HF dissociation process of the 1:3 adduct was demonstrated by repeated powder X-ray diffractometry at room temperature (Fig. 9). The X-ray pattern of the sample changed gradually to a different one (curve (e)) over several tens of minutes. On TG measurement, the sample giving pattern (e) was found to correspond to the 1:2 adduct.

**IR Spectra**—The IR spectra of anhydrous theophylline, the monohydrate, and the 1:3 and 1:2 HF adducts are shown in Fig. 10(a)–(d). The spectrum of the 1:3 adduct exhibited three characteristic strong absorption bands at 3490, 3210 and 3115 cm⁻¹, which indicate the presence of hydrogen bonds between theophylline and HF. The two broad absorption bands between 2800—2000 cm⁻¹ may indicate the presence of a positively charged nitrogen atom in the 1:3 adduct molecule.

The IR spectrum of the 1:2 adduct was very similar to that of the monohydrate except for the absorption at 3485 cm⁻¹.

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**Fig. 11. Micrographs of Sulfanilamide 1:2 HF Adduct and Its Desorbed Form**

(a), 1:2 HF adduct (partially desorbed), 100 ×; (b), after desorption (standing at room temperature under atmospheric pressure), 100 ×; (c), lightly pulverized state of (b), 100 ×.
Particle Size Reduction by Desorption of HF from the HF Adducts

Desorption of HF from HF adducts of griseofulvin, sulfanilamide and theophylline occurred completely and each original medicinal compound was recovered. Optical and
scanning electron micrographs of samples obtained via the HF adducts and particle size distribution data are shown in Figs. 11, 12 and 13. From these results, it is clear that effective particle size reduction is possible.

Further, as is shown in Fig. 12(d), the external appearance of crystals of phenacemide obtained from its anhydrous HF solution revealed agglomerates that consisted of primary fine particles, which may be formed via the HF adduct, although adduct formation of phenacemide could not be confirmed because of low stability.

Conclusion

Griseofulvin, sulfanilamide and theophylline were confirmed to form HF adducts having combining ratios of 1:1 (griseofulvin:HF), 1:2 (sulfanilamide:HF) and 1:3 and 1:2 (theophylline:HF). The mechanisms of HF adduct formation are supposed to involve hydrogen bonding or dipole-induced dipole interaction. The particle size of each medicinal was effectively reduced by formation of the HF adduct and subsequent desorption of HF.

References and Notes