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Adsorption of Nicotinic Acid on the Porous Powders

Sang-Chul Shin† and Cheong-Weon Cho*

*†College of Pharmacy, *Drug Development Research Laboratory*
Chonnam National University, Kwangju 500-757, Korea

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니코틴 산의 다공성 분체 흡착

신상철† · 조정원*

*†전남대학교 약학대학, *약품개발연구소*

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Nicotinic acid was mixed with glass powders such as controlled pore glass (CPG), glyceryl controlled pore glass (GPG) and glass beads (GB) at room temperature. The physicochemical properties of nicotinic acid in the various mixtures were examined by differential thermal analysis, X-ray diffraction study, Infrared spectroscopy and BET gas adsorption measurements. The peak area at the melting point from the various mixtures of nicotinic acid and CPG was increased with an increase of nicotinic acid concentration while the broad peak area was remained unchanged in the DTA curve. As shown in the powder X-ray diffraction patterns, the crystalline peaks of nicotinic acid disappeared in mixture with CPG, suggesting the interaction of nicotinic acid and porous powders. It was found that the larger the content of CPG, the higher the ratio of an amorphous state to a crystalline state. BET isotherm showed that as the amount of nicotinic acid was increased, the specific surface area was reduced proportionally to nicotinic acid content of up to 40% and remained constant thereafter. Sublimation of nicotinic acid from the mixture of nicotinic acid and CPG was examined. A large quantity of nicotinic acid was retained in the mixture when stored on various temperatures in vacuo for 10 hours. The nicotinic acid mixtures with CPG or GPG showed a high dissolution rates of nicotinic acid in aqueous solution, especially in the initial dissolution stage. CPG is expected to be a good pharmaceutical excipient to reduce the crystallinity of drugs and to prevent sublimation of drugs.

Keywords — Nicotinic acid, Controlled pore glass, Glyceryl controlled pore glass, Glass beads

There have been many studies on the molecular interactions between medicinals and pharmaceutical adsorbents such as aluminum silicate, activated carbon and anhydrous silicic acid.[1-6]

Many methods have been proposed for making drugs amorphous, for example, rapid cooling of melts to a glassy state[7], spray-drying, grinding with microcrystalline cellulose or with cyclodextrins and solid dispersion in polyvinylpyrrolidone or in polyethylene glycol.[8] Some organic crystalline drugs, when mixed with adsorbents such as magnesium aluminum silicate and treated at reduced pressure, readily become amorphous and this change can improve the dissolution characteristics of poorly water-soluble drugs.[9] For example, some organic crystalline medicinals such as aspirin and phenacetin, when mixed with an adsorbent, gradually became amorphous during storage at room temperature.[10]

Porous glass has numerous fine pores of 10 to 1000 Å in diameter and has been used in many applications ; for example, desalting of sea water[11], separation of hydrogen[12] and a catalyst carrier[13] as well as studies of superconductivity[14] and photochemical reactions.[15] CPG is used as

† To whom correspondence should be addressed.

a model porous material since there are many types having different pore diameters and chemical surface characteristics on the market and the properties of CPG are well known. CPG is well known for their large surface area and highly porous structures. CPG having narrow and regulated pore size distributions is commercially available.[16,17] The surface of glyceryl controlled pore glass (GPG), hydrophilic and non-ionic coating (covalently bonded) compatible with aqueous and most polar solvent systems, is chemically modified to block its slight negative charge.

In the present study, nicotinic acid that is soluble and liable to sublimate was mixed with porous adsorbents such as CPG, GPG and GB at room temperature and the physicochemical properties of the nicotinic acid in the mixtures were examined by differential thermal analysis, X-ray diffraction, IR spectroscopy, BET gas adsorption instrument and scanning electron microscope.

Experimental

Materials

CPG, GPG, GB and nicotinic acid were purchased from Sigma (U.S.A.). All chemicals of reagent grade were used as received without further purification.

Apparatus

UV spectrophotometer (Vectra ES/12, Hewlett Packard, U.S.A.), microbalance (Mettler AJ100, Switzerland), SEM (JSM 100, Japan), ultrasonic generator (Nihonseiki, Kaisha LTD.,Japan), thermal analyzer (SSC 5200, Seiko, Japan), BET gas adsorption instrument (Lab-made, Korea), X-ray diffractometer (Rigaku, Japan), dissolution tester (Hanson research corp., U.S.A.) and IR spectrophotometer (Perkin-Elmer 783) were used.

Preparation of Physical Mixtures

Nicotinic acid and adsorbents such as CPG, GPG and GB were weighed accurately in various proportions, mixed thoroughly by light trituration in a glass mortar and passed through a 50 mesh screen.

Measurement of Physicochemical Properties

To determine the physicochemical property of nicotinic acid, X-ray diffraction patterns, IR absorption spectra, differential thermal analysis thermograms and particle morphology were obtained.

Thermal Analysis

The samples of the mixtures were sealed into alumina sample pans and measured with TG / DTA analyzing instrument.[18] Temperature was calibrated using indium (156.6℃) as standards. The operating conditions in an open-pan system were as follows : sample weight, 5-10 mg ; heating rate, 20℃/min under an atmosphere. The temperature was increased from 20℃ to 600℃, then allowed to decrease to 20℃.

Powder X-ray Diffraction Study

Powder X-ray diffraction patterns[19] were measured using a Rigaku diffractometer with Ni filtered Cu-K_2 radiation. Measurement conditions were as follows : voltage, 30kv ; current, 5 mA ; scanning speed, 4°/min.

Infrared Spectroscopy

IR spectra were taken by the KBr method using IR spectrophotometer. A thin disc of the sample was prepared by grinding a nicotinic acid and the mixture with CPG in potassium bromide followed by compression on a carver press. The disc was placed in the sample beam and the spectrum was recorded from 4000 to 200 cm^{-1}.

Measurement of Specific Surface Area[20]

The specific surface area (S_w) was measured with a gas adsorption instrument by using Brunauer-Emmett-Teller (BET) gas adsorption one-point measurement method. Samples were activated using a sample tube in a thermos flask at 200℃ for 2 hours. After cooling a sample tube, it was soaked into a thermos flask of liquid nitrogen. Dead volume was measured in triplicate by infusing pure He gas. After pulling

out all He gas, the amount of adsorbed gas was measured by infusing N_2 gas and adsorbed amount of nicotinic acid was calculated by BET equation.

Scanning Electron Microscopy[21]

Particle shape was inspected by scanning electron microscope to facilitate the comparison between nicotinic acid and adsorbents such as CPG or GB in the mixture. The samples were coated with gold, using a direct current sputter technique. A SEM was carried out at an accelerating voltage of 25 Kv at 500-fold or 1,000-fold magnification.

Sublimation Test[6]

Nicotinic acid and the mixture of 30% nicotinic acid and 70% CPG were stored at various temperatures of 40, 100, 150, 200 and 250°C in vacuo for 10h. Remaining amount of nicotinic acid was determined at 264 nm by UV spectrophotometer.

Measurement of the Concentration of Nicotinic Acid

Accurately weighed CPG-nicotinic acid mixture was dispersed in 10 m*l* of mixed solution (0.1N HCl:ethyl alchol=35:65 v/v) and sonicated. The suspension was centrifuged and the supernatant solution was passed through a Millipore filter (0.45 μm). The concentration of nicotinic acid was determined spectrophotometrically at 264 nm.

Determination of Adsorption of Nicotinic Acid on CPG in Solution[17,22-25]

70 mg of nicotinic acid was dissolved in 100 m*l* of mixed solution (0.1 N HCl:ethyl alcohol=35:65 v/v) and the absorbance determined by spectrophotometer at 264 nm and used for adsorption test. 700 mg of CPG was added to the above sample solution and stored at 37°C for 1 day, filtered by a Millipore filter (0.45 μm) and tha absorbance was determined by spectrophotometer. As a control, the sample solution not added CPG was done by the same process. The difference in concentration before and after adding CPG was calculated as a drug adsorbed.

Dissolution Test[26]

Dissolution test was carried out by the USP basket method. The release of drug from the mixtures was determined using dissolution tester with 900 m*l* of distilled water at 37±0.5°C and 100 rpm. The amount of drug released was determined spectrophotometrically at 264 nm. Aliquots of 4 m*l* were withdrawn at various time intervals and replaced by fresh medium for corrections in the calculations. The data were plotted using the following equation to compensate for the portion of the drug removed from the dissolution flask at each withdrawl of the samples for concentration determination :

$$C_{corr} = C_{read} + \frac{4}{900}\sum_{s=1}^{n-1} C_{uncorr}$$

where, C_{corr} = corrected concentration of the sample at time 't',

C_{read} = spectrophotometrically measured concentration at time 't',

$\sum_{s=1}^{n-1} C_{uncorr}$ = sum of the uncorrected concentration of the previous runs,

$\frac{4}{900}$ means 4 m*l* of the sample withdrawn from the 900 m*l* of the dissolution medium

Results and Discussion

Thermal Behaviours of Nicotinic Acid and Its CPG Mixture

To clarify the differences in solid state properties of the physical and titurated mixtures, thermal analysis were performed using DTA/TG instrument.

Figure 1 shows the DTA curves of the nicotinic acid and the various mixtures of nicotinic acid and CPG. The DTA curve of the nicotinic acid showed an endothermic peak at 236.6°C showing the melting point of nicotinic acid and the subsequent endothermic peak at 276.6°C due to decomposition showing the weight loss of 100%

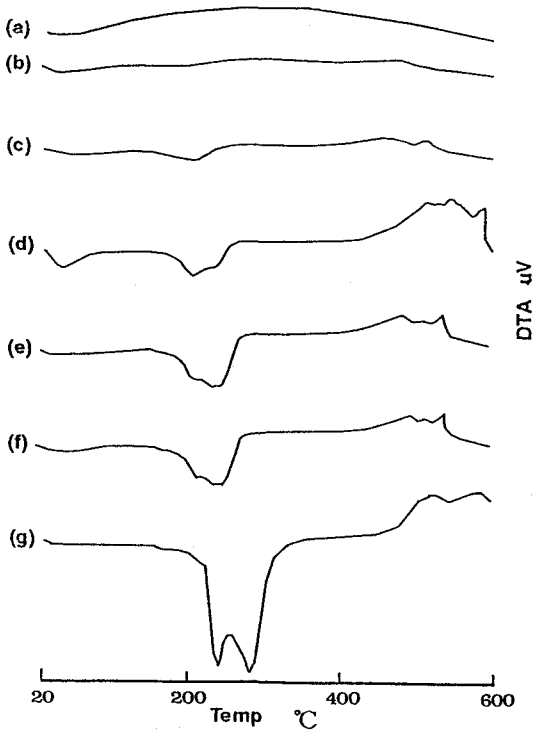


Figure 1—DTA curves of the various mixtures of nicotinic acid and CPG. Key : (a) : CPG, (b) : 1:9, (c) : 2:8, (d) : 3:7, (e) : 4.5:5.5, (f) : 5:5, (g) : nicotinic acid

on the TGA curve. The DTA curve of the CPG showed a very weak endothermic peak at 25℃ with a weight loss of about 17.4% on the TG curve. The mixture containing 10% nicotinic acid showed a small broad endothermic peak at about 27.8-54.9℃ but no peak was found at 236.6℃, the melting point of nicotinic acid. In the mixture containing 30% nicotinic acid, two endothermic peaks were observed at 26.5-72.1℃ and 161.5-247.2℃. The endothermic peak area at 27.8-54.9℃ increased with increasing ratio of nicotinic acid, while that at 161.5-247.2℃ remained unchanged.

Table I shows the DTA parameters and characteristic temperature for various mixtures of nicotinic acid and CPG. As the ratio of CPG was increased, DTA peak temperature and onset temperature were decreased with decreased value of enthalpy.

Figure 2 shows the DTA curves of the nicotinic

Table I—*DTA Parameters and Characteristic Temperature for Various Mixtures of Nicotinic Acid and CPG.*

Ratio	DTA peak temp (℃)		Onset temp	Enthalpy (μV · s/mg)
10:0	249.0	271.9	198.1	518
8:2	245.9	257.6	196.6	386
5:5	223.7	239.7	194	303
4.5:5.5	222.5	238.7	192.7	294
3:7	221.2	235.6	177.1	148
2:8	219.8	234.1	166.8	93

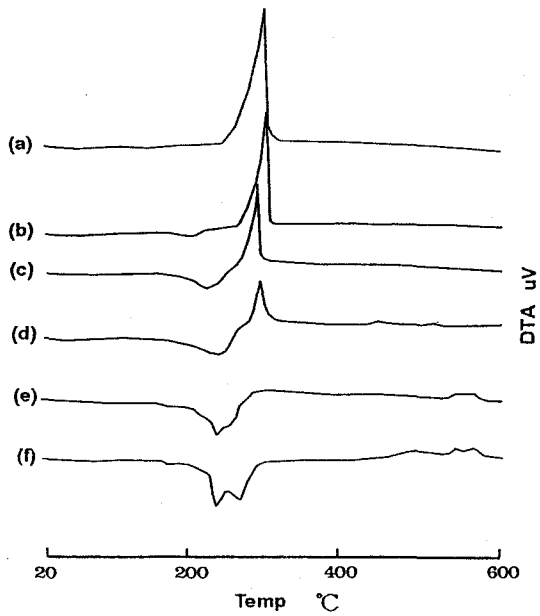


Figure 2—DTA curves of the various mixtures of nicotinic acid and GPG. Key : (a) : GPG, (b) : 1:9, (c) : 4:6, (d) : 5:5, (e) : 8:2, (f) : nicotinic acid

acid and the various mixtures of nicotinic acid and GPG. The DTA curve of the nicotinic acid showed an endothermic peak at 236.6℃ showing the melting point of nicotinic acid and the subsequent endothermic peak at 276.6℃. The DTA curve of the GPG showed a strong exothermic peak at 230-300℃ with a weight loss of about 15% due to the decomposition of the functional group of glyceryl on the TGA curve. The endothermic peak area at the melting point was increased and the peak became broad and the melting point was lowered with the increasing ratio of CPG. On the other hand, the DTA curves of the nicotinic a-

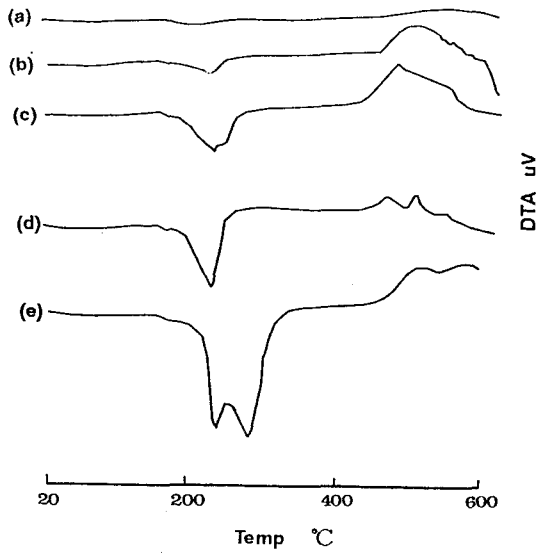


Figure 3—DTA curves of the various mixtures of nicotinic acid and GB. Key : (a) ; GB, (b) ; 1:9, (c) ; 4:6, (d) ; 5:5, (e) ; nicotinic acid

cid-GB mixture showed only one endothermic peak of irregular shape corresponding to the melting of the nicotinic acid (Figure 3).

These DTA results show that three different states of nicotinic acid may exist in nicotinic acid-CPG mixtures, that is, (1), the crystalline state (2), the state which shows the broad endotherm at a lower temperature than the melting point and (3), the state which does not show a peak on the DTA curve.

As the mixture of nicotinic acid and GB showed only melting of the crystals, it is thought that the pores of CPG might play an important role in these phenomena.

Crystalline Fraction Ratio

Figure 4 shows the relationship between crystalline fraction ratio of nicotinic acid and percentage of adsorbents such as CPG and GB. A crystalline fraction ratio of nicotinic acid in mixtures with adsorbents is smaller than 1.0.

This implies that an interaction between the functional group of silanol on the surface of the adsorbents and the molecule of nicotinic acid may exist and part of the crystal turns to amorphous form.

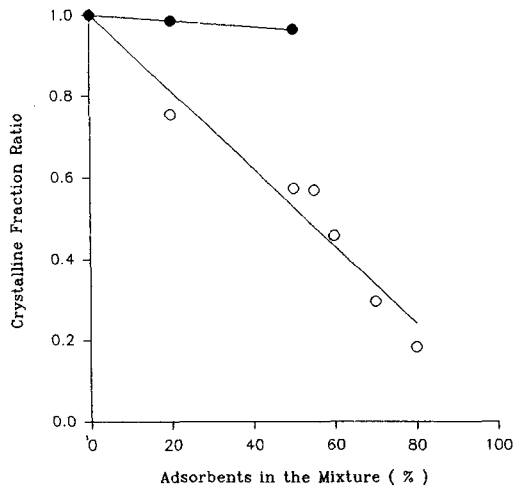


Figure 4—Relationship between crystalline fraction ratio of nicotinic acid and the adsorbents added. Key : ○ ; CPG, ● ; GB

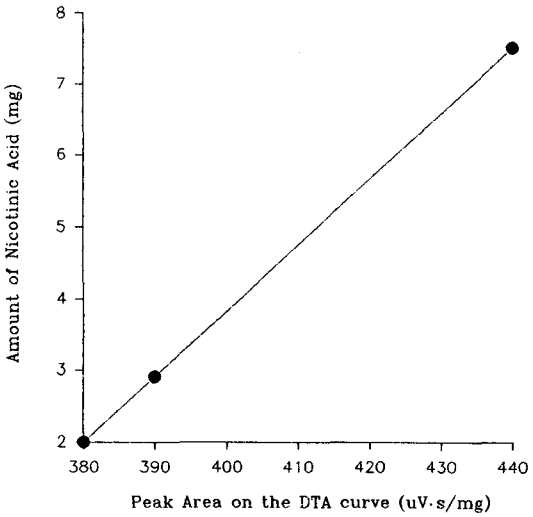


Figure 5—Linear relationship between the amount of nicotinic acid and peak area in the DTA peak.

Quantitative Analysis of Nicotinic Acid in the Three Phases

The quantities of the three phases in mixtures were obtained from the thermograms. Figure 5 shows the linear relationship between the amount of nicotinic acid and the peak area on the thermograms.

The quantity of phase 1, m_1, can be calculated from the peak area at the melting point by using the linear relationship. The quantity of phase 2, m_2, can be calculated by measuring

the broad peak area at lower temperature on the assumption that the specific heat of melting is equal to that of crystals. The quantity of phase 3, m_3, can be calculated as $m_3=m-(m_1+m_2)$, where m is the total amount of nicotinic acid in the mixture.

Figure 6 shows the relationship between total amounts of nicotinic acid added to 1 mg of CPG and the calculated amounts of the three phases. The calculated amount of phase 1 was zero up to 0.8 mg of nicotinic acid and then increased linearly with an increase of the added amounts. In contrast with phase 1, the calculated amount of phase 2 increased sharply up to 1.0 mg of nicotinic acid and thereafter increased slowly to reach a constant value and that of phase 3 had a large value even at a low content of nicotinic acid and immediately reached a constant value on further addition of nicotinic acid.

The specific heat of melting of phase 2 may be smaller than that of the crystals since lattice disorder is presumed to exist from the DTA and X-ray diffraction patterns. The amount of phase 2, therefore, may be somewhat larger than the calculated value. However, these results lead to the conclusion that nicotinic acid is in phase 2 and 3 in the pores of CPG at room temperature when a small amounts of nicotinic acid are added to CPG. When a large amounts of nicotinic acid are added to CPG, the excess amounts of nicotinic acid are in phase 1, which probably exist outside of the pores. When such samples were cooled down and a second DTA measurement was carried out, a phase change was no longer recorded on the thermograms.

It is expected that the volatile drug in phase 3 is physically adsorbed, tightly on the pore walls.

Changes in the Powder X-Ray Diffraction Patterns

Powder X-ray diffraction patterns of the mixture of nicotinic acid with CPG or GB are shown

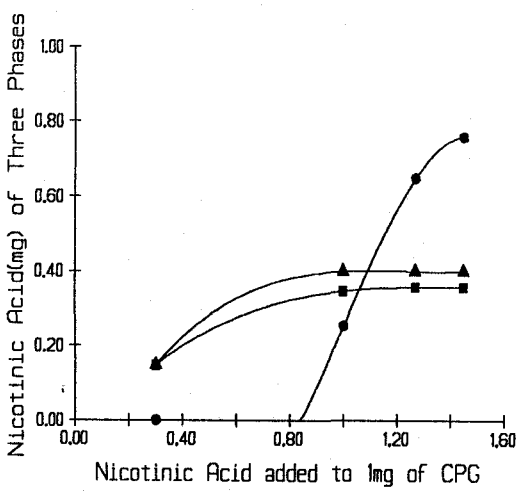


Figure 6—Relationship between total amount of nicotinic acid and calculated amount of the three phases. Key : ● : phase 1, ■ : phase 2, ▲ : phase 3

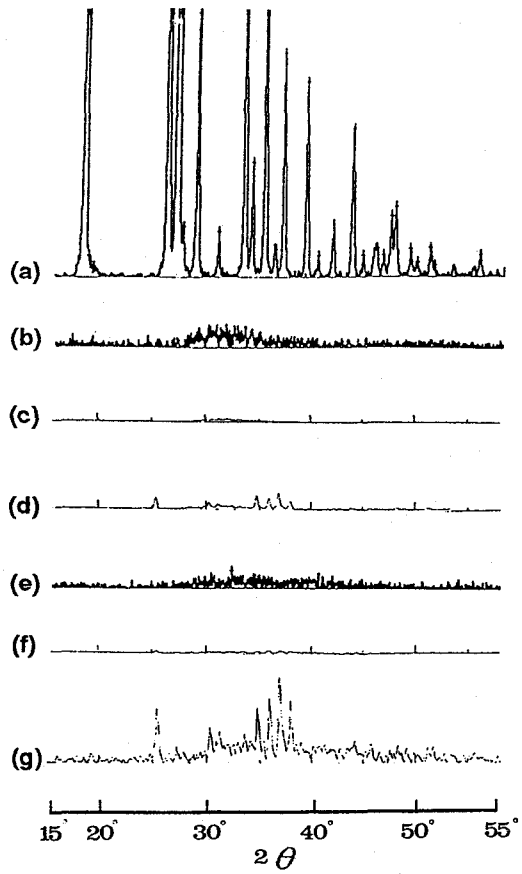


Figure 7—Comparison of X-ray diffraction patterns. Key : (a) : nicotinic acid, (b) : CPG, (c) : 1:9 nicotinic acid-CPG, (d) : 3:7 nicotinic acid-CPG, (e) : GB, (f) : 1:9 nicotinic acid-GB, (g) : 3:7 nicotinic acid-GB

in Figure 7. Nicotinic acid showed significant diffraction peaks at about 15.4, 20.3, 24.7, 25.9, 26.8 and 27.9 as 2θ degree, while CPG and GB show no crystalline peaks indicating the amorphous form. As shown in X-ray diffraction patterns from the various mixtures of nicotinic acid and CPG or GB, the crystalline peaks of nicotinic acid were quite different. The crystalline peaks of nicotinic acid from the 1:9 mixture of nicotinic acid and CPG or GB disappeared, showing their change to amorphous form. The crystalline peaks of nicotinic acid from the 3:7 mixtures with GB still remained, but those with CPG to a greater extent disappeared.

As shown in the powder X-ray diffraction patterns, the crystalline peaks of nicotinic acid disappeared in mixture with CPG, suggesting the possible interaction of nicotinic acid with porous powders.

Molecular Behaviour of Nicotinic Acid in a Mixture with CPG

When nicotinic acid was mixed with CPG at a low concentration, the mixtures did not show the heat of melting or X-ray diffraction peaks, showing the absence of crystalline state.

At 20% concentration of nicotinic acid, a broad endothermic peak was observed at lower temperature than the melting point. At 45% concentration of nicotinic acid, an endothermic peak at the melting point appeared in addition to the broad peak. The peak area at the melting point (Figure 1) increased with higher concentration of nicotinic acid, while the peak area at lower temperature (161.5~247.2℃) did not change. From these results, three phases of nicotinic acid exists in nicotinic acid-CPG mixtures.

The first is the crystal phase (phase 1), the second is the phase that shows the broad peak at lower temperature than the melting point of the crystal (phase 2) and the last is the phase undetectable by the DTA and X-ray diffraction methods (phase 3).

IR Spectra of Nicotinic Acid and the Mixture of the Nicotinic Acid and CPG

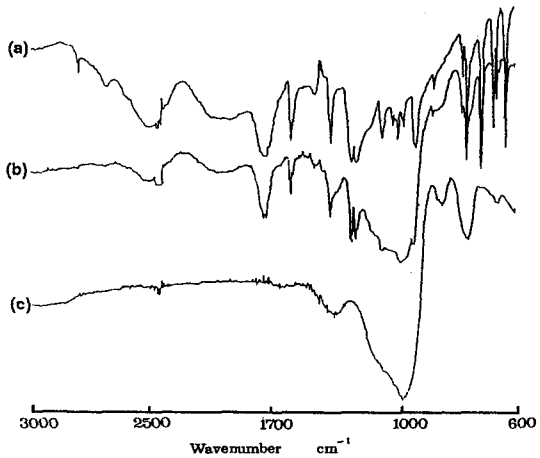


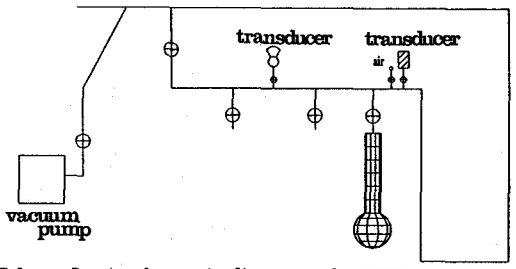
Figure 8—Comparison of infrared spectra. Key : (a) ; nicotinic acid only, (b) ; 3:7 nicotinic acid-CPG, (c) ; after DTA test of (b) sample

Figure 8 shows the IR spectra of the nicotinic acid and the 3:7 mixture of nicotinic acid and CPG before and after DTA measurement. The IR spectrum of the nicotinic acid showed the absorption band at 1700 cm^{-1} attributable to the carbonyl group. The carbonyl streching vibration was also shown from the 3:7 mixture of nicotinic acid and CPG. This means that the interaction between nicotinic acid and CPG might be a physical adsorption. From the IR spectra of the heated CPG mixture, nicotinic acid is considered to be decomposed at high temperature.

Measurement of the Specific Surface Area[22,23]

Based on the DTA results, it can be said that nicotinic acid may occupy the pore of CPG in the physical mixture of nicotinic acid and CPG.

Specific surface area of test samples was measured by BET gas adsorption instrument (Scheme I). BET isotherm was obtained (Figure 9 & 10) by calculating the specific surface area. The specific surface area of various mixtures is shown in Table II. The specific surface area of CPG before mixing with nicotinic acid was about 108.15 m^2/g. The specific surface area of various mixture of nicotinic acid and CPG was 79.94 m^2/g in the 1:9 ratio, 55.82 m^2/g in the 2:8 ratio, 7.31 m^2/g in the 4:6 ratio. The



Scheme I—A schematic diagram of a BET gas adsorption instrument

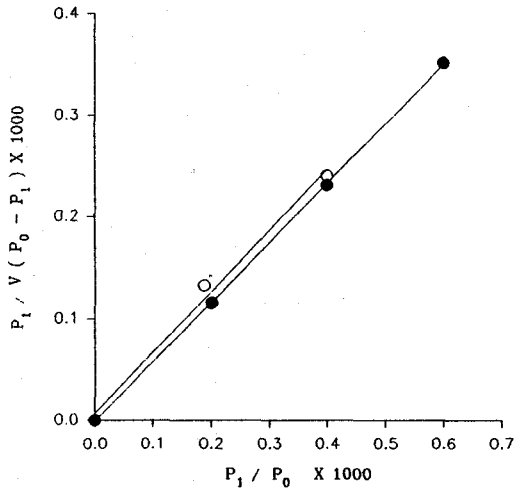


Figure 9—BET isotherms of various nicotinic acid-CPG physical mixtures. Key : ○ ; 2:8 ratio, ● ; 4:6 ratio

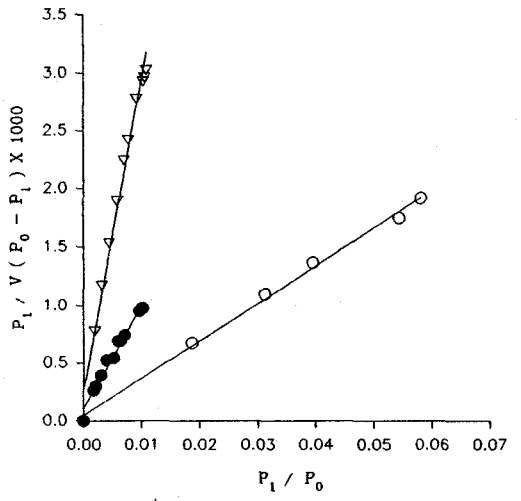


Figure 10—Comparison of BET isotherm of various nicotinic acid-CPG physical mixture. Key : ○ ; CPG, ● ; 1:9 ratio, ▽ ; 5:5 ratio

specific surface area was reduced proportionally to nicotinic acid content of up to 40% and remained almost constant thereafter (Figure 11). The mixture having no crystalline peaks in the X-ray diffraction patterns showed an appreciable decrease in the surface area (Figure 7).

Table II *Specific Surface Area for the Various Mixtures of Nicotinic Acid*

Mixture ratio	Specific surface area(m^2/g)
CPG alone	108.15
1:9	79.94
2:8	55.82
4:6	7.31
5:5	7.18

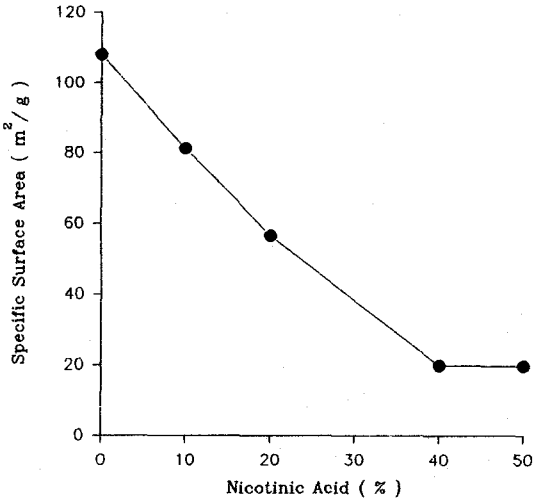


Figure 11—Specific surface area of CPG depending on the percent of the nicotinic acid.

From these results, it is suggested that nicotinic acid might be adsorbed physically on the pores of CPG in the mixture.

Observation of Particle Behaviour

Figure 12 shows the scanning electron micrographs of nicotinic acid, CPG and GB. Morphology of the mixture of 10% nicotinic acid and 90% CPG or GB is shown in Figure 13. Nicotinic acid and GB are present apart from the mixture of 10% nicotinic acid and 90% GB but morphology of the mixture of 10% nicotinic acid and 90% CPG is quite different, suggesting the entrapment of nicotinic acid into the pore of CPG.

Adsorption of Nicotinic Acid on CPG in Solution

The interaction between nicotinic acid and

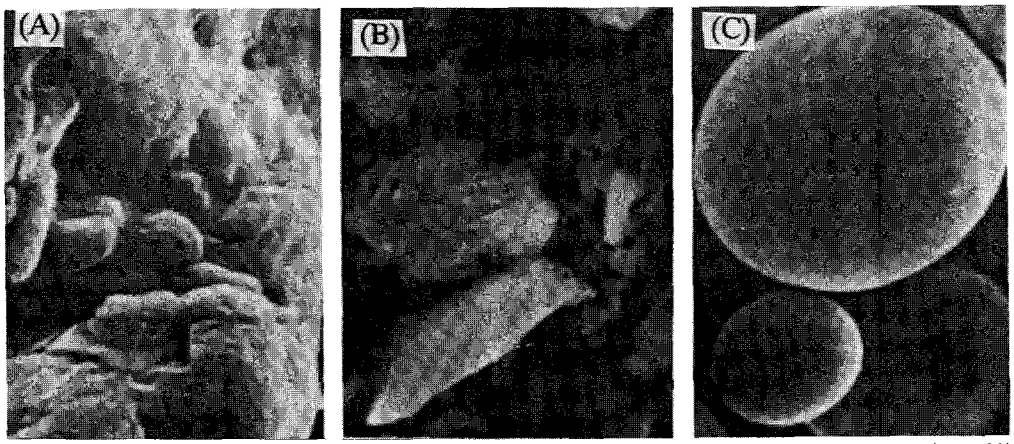


Figure 12—Scanning electron micrographs of nicotinic acid, CPG and GB. Key : (A) ; nicotinic acid (×1,000), (B) ; CPG (×1,000), (C) ; GB (×500)

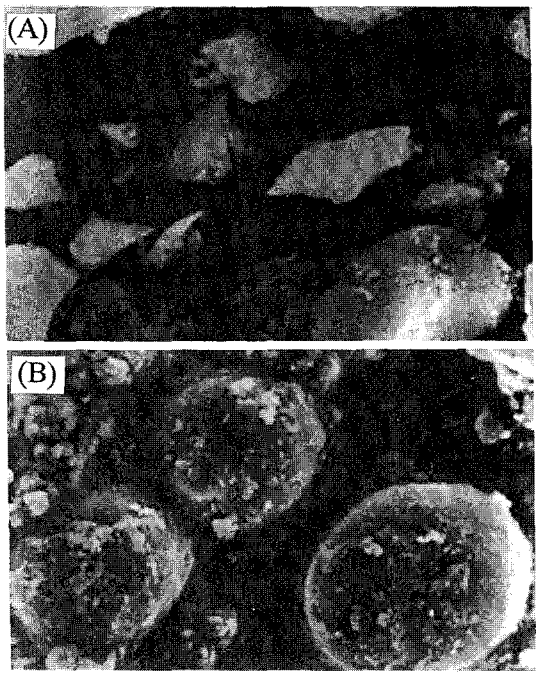


Figure 13—Scanning electron micrographs of the mixture of 10% nicotinic acid and 90% CPG and GB. Key : (A) ; 1:9 nicotinic acid-CPG (×1,000), (B) ; 1:9 nicotinic acid-GB (×500)

CPG present at the powder state is presumed to be due to physical adsorption.

To investigate the interaction in solution state, the following experiments were conducted. The concentration of nicotinic acid after storing the sample solution at various conditions for 24 hours was determined. The concentration of nicotinic acid was almost same even through CPG was added. From this result, the adsorption of nicotinic acid to CPG in solution was not present.

Table III—*Remaining Percent of Nicotinic Acid Stored on the Various Temperature*

Temp (°C)	Initial amount(mg)	Remaining amount(mg)	Remaining (°C))
40	9.9	9.9	100
100	9.9	9.9	100
150	9.9	9.8	98.9
200	9.9	7.6	76.8
220	9.9	4.2	42.4
250	9.9	0	0

Table IV—*Remaining Percent of Nicotinic Acid from the 3:7 Nicotinic Acid-CPG Mixture Stored on the Various Temperature*

Temp (°C)	Initial amount(mg)	Remaining amount(mg)	Remaining (°C))
40	12.0	11.7	97.5
100	12.6	11.9	94.4
150	12.4	11.6	93.6
200	12.4	9.0	72.6
250	11.8	9.0	65.3

Effect of CPG on Sublimation of Nicotinic Acid

Table III and IV show the remaining percent of nicotinic acid from nicotinic acid itself and the 3:7 mixture of nicotinic acid and CPG stored at various temperature in vacuo for 10h.

In case of nicotinic acid, the remaining percent of nicotinic acid was 100% at 40°C and

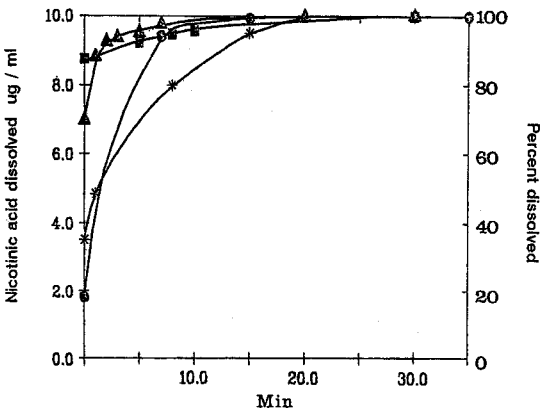


Figure 14—Releasing patterns of nicotinic acid from the 3:7 mixture of nicotinic acid and various adsorbents. Key : ○ ; nicotinic acid, ● ; CPG, ▽ ; GPG, ▼ ; GB

100°C, 98.9% at 150°C, 76.9% at 200°C, 42.4% at 220°C, 0% at 250°C. On the other hand, in case of the mixture of 30% nicotinic acid and 70% CPG, the remaining percent of nicotinic acid was 97.5% at 40°C, 94.4% at 100°C, 93.6% at 150°C, 72.6% at 200°C, 65.3% at 250°C. Different phenomena with the interaction of solution state between nicotinic acid molecule and the pore wall were observed by sublimation study.

It is supposed that the CPG as an adsorbent suppresses the sublimation of nicotinic acid.

Dissolution Behaviours of Nicotinic Acid

Release patterns of nicotinic acid from the 3:7 ratio mixture of nicotinic acid and adsorbents such as CPG, GPG or GB are shown in Figure 14. Dissolution rate of nicotinic acid was increased from the mixture of nicotinic acid and CPG or GPG. Initial dissolution rate of nicotinic acid was slightly increased from the mixture of nicotinic acid and CPG.

It is suggested that nicotinic acid present as a non-crystalline form might be dissolved rapidly.

Conclusions

The present investigation on the interaction of nicotinic acid and porous powders showed the following results.

1. From the results of thermal analysis and X-ray diffraction study of various physical mixtures of nicotinic acid and CPG, it might be said that nicotinic acid was changed to a non-crystalline form.

2. BET isotherm showed taht as the amount of nicotinic acid was increased, the specific surface area of CPG-nicotinic acid mixtures was reduced proportionally to nicotinic acid content of up to 40% and remained constant thereafter.

3. The pores of CPG play an important role in the following three different states of nicotinic acid in nicotinic acid-CPG mixture.

(1) the crystalline state,

(2) the state which shows the broad endotherm at lower temperature than the melting point

(3) the state which does not show a peak on the DTA curve.

4. The interaction between nicotinic acid and CPG was supposed to be a physical adsorption.

5. Initial dissolution rate of nicotinic acid was slightly increased with the mixture of nicotinic acid and CPG or GPG.

6. CPG is expected to be a good pharmaceutical excipient to reduce the crystallinity of drugs and to prevent sublimation of drugs.

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