Diffusion and Reaction of p-Nitroaniline and Succinic Anhydride in Controlled Pore Glass

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A multi-layered tablet which consisted of controlled pore glass (CPG) and organic compounds was prepared. Addition reactions between succinic anhydride and p-nitroaniline, which were included separately in the CPG layers of the multi-layered tablet, have been studied. The reaction product, succinyl-p-nitroanilide, was mainly distributed near the p-nitroaniline layer. This can be explained in terms of a higher diffusion rate of succinic anhydride, resulting in its higher vapor pressure. The diffusion rate constant of succinic anhydride in the CPG120 system was estimated as $6.00 \times 10^{-7}$ cm²/s by fitting the diffusion equation to experimental results.

Keywords: controlled pore glass; solid state reaction; addition reaction; diffusivity; layered cylindrical tablet; succinic anhydride; p-nitroaniline

Introduction

We have already investigated the interaction between medicinals and controlled pore glasses (CPGs). In the previous paper, we reported that the crystalline characteristics of medicinals were changed by mixing them with CPG, and that the solid-state addition reaction between succinic anhydride and p-nitroaniline was also accelerated in the CPG mixture. A possible mechanism was proposed by Pikal et al., for the diffusion of medicinals in the mixed powder systems with CPG, i.e., gas-phase diffusion with capillary condensation. In practice, however, it was difficult to clarify the mechanism of diffusion of medicinals with chemical reactions in the mixture with CPG. The triple (double) layered cylindrical tablet appeared to be a useful model for studying the diffusivity of medicinals in CPG, because of simple geometry and the constant area of interface during the reaction. The present investigation was undertaken to examine the diffusivity of medicinals in CPG with a triple (double) layered cylindrical tablet, and to clarify the mechanism leading to the amorphous state of medicinals in CPG system.

Experimental

Materials

Succinic anhydride (Wako Pure Chemical Industries Co., Ltd.) and p-nitroaniline (Wako Pure Chemical Industries Co., Ltd.) were of reagent grade and used as received from the supplier. Both crystals were used after sieving (120/250 mesh). CPGs were obtained from Electro-Nucleonics Ltd., CPG120 (mean pore diameter: 117Å, specific surface area: 119 m²/g) and CPG1000 (mean pore diameter: 962 Å, specific surface area: 26.1 m²/g) were used after drying in a vacuum at 120°C for 3 h.

Preparation of Tablets

For the p-nitroaniline-CPG-succinic anhydride triple layered tablet system (tablet diameter: 10.0 mm, total thickness: 6.1 mm), p-nitroaniline (200 mg) and succinic anhydride (200 mg) were compacted at 0.4 ton/cm² using dies and plane-faced punches, respectively, with a hydraulic press (Riken Seiki, P-1B). A tablet of p-nitroaniline was placed in the bottom of the die, then CPG (500 mg) was added on the tablet. A previously cast succinic anhydride tablet was also placed above the CPG layer and compacted using the same pressure (Chart 1A). For the succinic anhydride-CPG double layered tablet system (tablet diameter: 10.0 mm, total thickness: 5.5 mm), first p-nitroaniline was mixed with CPG in the mixing ratio of (90% CPG120+10% p-nitroaniline), or (95% CPG1000+5% p-nitroaniline). The mixtures were stored for a week in a desiccator at 0% relative humidity (RH) and 50°C. A tablet of succinic anhydride was first prepared in the bottom of the die, then the mixture of p-nitroaniline with CPG was added and compacted under the same pressure (Chart 1B).

Measurement of Concentration of Succinyl-p-nitroanilide (Product) in Samples

After compression of the tablet, the die without ejection of the tablet was stored in a desiccator at RH 0% and 50°C. At the appropriate time intervals up to 70 h, the die with tablet was taken out from the desiccator. After ejection of the tablet from the die, the tablet was cut with spacing of 0.5—1.0 mm from the interface and each fraction was collected. To determine the amount of reaction product in each fraction, the powder samples were suspended in a 50% aqueous ethanol solution completely to extract succinyl-p-nitroanilide. The concentration of succinyl-p-nitroanilide was determined spectrophotometrically at 322 and 384 nm on a Shimadzu double-beam spectrophotometer UV-2000.

Results and Discussion

Diffusivity Studies

The prepared triple layered tablet was stored at 50°C and RH 0%. In this storage condition, the decomposition rates of organic compounds were negligible. Figure 1 shows the variations of succinyl-p-nitroanilide distribution in the CPG120 layer as a function of storage time. The abscissa is the distance from the interface with the p-nitroaniline tablet, and the ordinate is the concentration of reaction product in CPG120. Succinic anhydride and p-nitroaniline diffused into the CPG120 layer from the right and left sides respectively, and the reaction of succinic anhydride and p-nitroaniline was developed in the CPG layer. The concentration of the reaction product, succinyl-p-nitroanilide, increased with the elapse of storage time, and the maximum concentration of the reaction product was observed close to the p-nitroaniline interface. Good reproducibility of the concentration profiles of the reactant product was observed for different preparations. This suggests that the diffusivity of succinic anhydride in CPG120 was greater than that of p-nitroaniline. The gaseous...
flux of a sublimating organic compound from the crystal surface depends on many factors such as temperature, vapor pressure and surface area of organic crystals. Table I shows the vapor pressure of succinic anhydride and p-nitroaniline crystal at 100°C. The vapor pressure of succinic anhydride was about 100 times greater than that of p-nitroaniline at 100°C. This should account for the high diffusivity of the succinic anhydride in CPG120. In this experimental system, temperature and surface area of the tablet of succinic anhydride and p-nitroaniline were constant, hence the difference of the vapor pressure of the succinic anhydride and p-nitroaniline crystal was considered to cause the difference in diffusivity, although the molecular weights and collision cross-section of each compound might also have some effect on the diffusivity. To investigate the above results more clearly, we studied a simple system, i.e., a double layered tablet of succinic anhydride and CPG containing 10 or 5% p-nitroaniline. Figure 2 shows the concentration profiles of the reaction product in the CPG120 double layered tablet containing 10% p-nitroaniline (Chart 1B) after storage at 50°C and RH 0% for 48h. The concentration of succinic-p-nitroaniline increased with the elongation of storage time, and in the distance within 1.5 mm, the saturated concentration of 7.0 x 10^{-7} mol/mg of CPG was observed after storage for 48 h. The succinic-p-nitroaniline concentration of this level was reasonable as the initial concentration of p-nitroaniline (one of the reactants) in the mixture was calculated as 7.0 x 10^{-7} mol/mg of CPG, indicating the completion of an addition reaction between diffusion succinic anhydride and p-nitroaniline.

The concentration profiles of succinic-p-nitroaniline in the CPG100 of the double layered tablet (Chart 1B) after storage at 50°C and RH 0% are shown in Fig. 3. The final concentration saturation level of succinic-p-nitroaniline was just half of the CPG120 mixture, as the initial p-nitroaniline concentration was 5% in this case. After storage for 24 h, the concentration of succinic-p-nitroaniline was observed even at the distance of 1.3 mm. From comparison with Fig. 2, the concentration of succinic-p-nitroaniline at 2.5 mm in the CPG1000 system was significantly higher than that in the CPG120 system. This difference seemed to be consistent with the differences in specific surface area, mean pore diameter of CPGs and adsorption energy of the medicinals on CPGs. Adsorption energy on CPG120 was greater than that on CPG1000, the small mobility of the adsorbed molecules on CPG120 might be associated with a large energy of bonding to the surface, in contrast to the higher mobility of weakly bound molecules on CPG1000. In most meso-porous materials, in which the pore diameter was less than 1000 Å, Knudsen diffusion was important in characterizing the total diffusion of gases. However, in micro-porous materials having pore diameters of less than 100 Å, the effect of the diffusion of adsorbed molecules along the internal surfaces of porous materials on the total diffusion could not be neglected. Therefore, it was suggested that the great adsorption energy on CPG120 correlated with the pore surface diffusion of succinic anhydride.

**Calculation of the Diffusivity** In the double layered
system, we can regard the addition reaction as a pseudo-first order reaction. If the diffusing substance is immobilized by an irreversible first-order reaction, the equation for diffusion in one dimension becomes \(^{15}\):

\[
\frac{\partial c}{\partial t} - D \frac{\partial^2 c}{\partial x^2} = -k \cdot c
\]  

(1)

where \(c\) is the concentration of succinic anhydride, \(t\) is the storage time, \(x\) is the distance from the interface between succinic anhydride and CPG, \(D\) is the diffusivity of succinic anhydride in CPG and \(k\) is the reaction rate constant between succinic anhydride and \(p\)-nitroaniline in CPG. The initial conditions for above system are:

\[
c = c_0, \quad x > 0
\]

\[
c = 0, \quad x = 0
\]

Since succinic anhydride does not reach the outer end of the CPG subtablet, the system may be considered as a seminfinite rod with boundary conditions. The boundary conditions are:

\[
c = c_0 \quad \text{at} \quad x = 0
\]

\[
c = 0 \quad \text{at} \quad x = +\infty
\]

Dimensionless concentration \(C'\), time \(T\) and distance \(X'\) variables, are defined as follows:

\[
C' = \frac{c}{c_0}
\]

\[
T = c_0 \cdot k \cdot t
\]

\[
X' = \frac{c_0 \cdot k}{D} \cdot x
\]

Equation 1 can be written in terms of dimensionless parameters as follows:

\[
\frac{\partial C'}{\partial T} = \frac{\partial^2 C'}{\partial X'^2} \cdot \frac{1}{c_0} \cdot C'
\]

(5)

Equation 5 with dimensionless parameters is convenient to calculate by computer. Then, the equation with boundary conditions are numerically solved for \(C'\) as a function of \(X'\) and \(T\). \(^{15}\) Since a small net size (\(\Delta T, \Delta X'\)) was necessary to obtain an accurate solution, the value of \(\Delta T\) was determined as \(5.0 \times 10^{-4}\).

The concentration ratio of succinyl-p-nitroanilide is plotted against the distance from the interface in Fig. 4 and the effect of diffusivity on concentration profiles is demonstrated. The initial concentration of succinic anhydride in CPG120 was calculated as \(1.00 \times 10^{-3}\) mol/cm\(^3\), and the first-order reaction rate constant between succinic anhydride and \(p\)-nitroaniline in CPG120 at 50 °C was determined as \(1.67 \times 10^{-4}\) cm\(^3\)/mol s, respectively. \(^{5}\) The concentration of reacted product at the distance (x) decreased with the decrease of the diffusivity.

Curves of the concentration ratio \((C')\) vs. distance from the interface (x) are shown for assumed values of \(D\) in Fig. 5 for comparison with the experimental value. Good agreement between theoretical and experimental concentration profiles is obtained when the diffusivity of succinic anhydride in CPG120 is estimated \(6.00 \times 10^{-7}\) cm\(^2\)/s. This value of diffusivity is smaller than the 0.33 cm\(^2\)/s observed in gas phase and 0.09 cm\(^2\)/s observed in meso-pore (170 Å) by Knudsen diffusion at 1 atm respectively. \(^{16}\)