Effect of polymorphism on crystallization of donepezil in drug-in-adhesive matrix

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ABSTRACT SUMMARY
The effects of crystalline form on crystallization of a drug in pressure sensitive adhesives were investigated using donepezil as a model drug. Four kinds of donepezil polymorphs, defined as Form A, B, C, and D, exhibited different crystalline characteristics. Depending on polymorphism, saturation solubility and induction time of crystallization in three different adhesive matrixes varied. The results were compared with drug solubility in water and organic solvent.

INTRODUCTION
Drug-in-adhesive (DIA) system is the most frequently used transdermal drug delivery system wherein drug is directly included in the pressure sensitive adhesive itself. It usually is thin, flexible and comfortable to the patients. In spite of these advantages of DIA, crystallization of the drug in adhesive matrix limited the development of DIA system. Crystallization is mostly due to supersaturation of a drug in the matrix, which means the amount of drug solubilized in the matrix is greater than its equilibrium solubility [1].

Many of drugs are solid and exist in more than one crystalline form or polymorphism. While polymorphs have the same chemical composition, they differ in their packing and geometrical arrangement, resulting in different physicochemical properties including melting point, chemical reactivity, solubility, and dissolution rate.

In the present study, we investigated the effects of polymorphism on the crystallization of donepezil in the adhesive matrix in terms of solubility in the adhesive matrix and induction time of crystallization.

EXPERIMENTAL METHODS
Preparation of patch containing donepezil
Drug solution was prepared by dissolving donepezil in ethyl acetate. After adding enhancer and PSA to the drug solution, the mixture was stirred using a teflon-coated magnetic bar. The resulting drug-PSA solution was coated onto a release liner. After the solvent had been removed, it was laminated with a polyester backing film (ScotchPak® 9720, 3M, USA). [2]

Differential scanning calorimetry (DSC)
Thermal analysis was carried out using a DSC unit (Pyris 6 DSC, Perkin-Elmer, Netherlands). All samples (2mg) were weighed and heated at scanning rate of 10°C/min between 20°C and 120°C. Indium was used to calibrate the temperature scale and enthalpic response.

Measurement of donepezil solubility in water or n-heptane
Excess amount of each donepezil polymorph was added in water or n-heptane. The suspension was stirred at room temperature for 48 hours. The saturated solution was filtered through a 0.45 µm nylon syringe filter. After appropriate dilution, the concentration of donepezil was determined by HPLC system (Shimadzu Scientific Instruments, MD), consisting of UV detector (SPD-10A), reversed-phase C18 column (4.6mm x 150mm, 5µm, Shiseido), a pump (LC-10AD), and an automatic injector (SIL-10A). The wavelength of UV detector was set at 271nm. The column temperature was maintained at 30°C and the flow rate was 1mL/min. The mobile phase consisted of 650 ml of 0.015M sodium 1-decanesulfonate aqueous solution containing 1ml of perchloric acid and 350 ml of acetonitrile.

RESULTS AND DISCUSSION
As shown in DSC thermogram, Form A and Form D had endotherm at 93.03°C, corresponding to the melting point of donepezil. Form B showed two peaks at 91.02°C and 95.02°C. In case of Form C, the peak was observed at 92.03°C (Fig. 1). The powder XRD patterns of donepezil are presented in Fig. 2. Form A and D showed similar pattern, while Form B and C exhibited clearly different pattern from Form A.

[Fig.1. Differential scanning calorimetric thermograms]
PXRD patterns of donepezil crystalline form

The solubility of donepezil was assessed in acrylic (Duro-Tak 87-2516) and acrylic rubber hybrid adhesive (Duro-Tak 87-502B and 87-503A:87-504A (1:1)). The minimum concentration at which crystal was formed within 120 days was taken as the solubility in the matrix. As represented in Table 1, the solubility varied depending on donepezil polymorph in 503A:504A (1:1) and 2516 matrix, however, no significant difference was observed in 502B. In 503A:504A (1:1) adhesive, form B had the lowest solubility. On the contrary, Form B had the highest solubility in 2516 adhesive.

Table 1. Solubility of donepezil in pressure sensitive adhesives

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>Concentration of donepezil (% w/w)</th>
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<tbody>
<tr>
<td></td>
<td>502B</td>
</tr>
<tr>
<td>A</td>
<td>10%</td>
</tr>
<tr>
<td>B</td>
<td>5.5%</td>
</tr>
<tr>
<td>C</td>
<td>10%</td>
</tr>
<tr>
<td>D</td>
<td>10%</td>
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</tbody>
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Donepezil solubility in water and n-heptane (n=3, AVE ± S.D.)

Fig. 3. Onset time of crystallization of donepezil in PSA depending on polymorphism

Fig. 4. Donepezil solubility in water or n-heptane (n=3, AVE ± S.D.)

CONCLUSION

Donepezil polymorphism had effects on crystallization of the drug in adhesive matrix. The solubility of the drug and crystallization induction time in the matrix also varied depending on polymorphism. This tendency of recrystallization was different depending on adhesive matrix. Correlation between solubility in adhesive matrix and other solvents was not observed.

REFERENCES
