

hydroxypropyl- $\beta$ -cyclodextrin (HPCD), a derivative of  $\beta$ -CD, is a highly water-soluble (> 100%, w/v) amorphous cyclodextrin, which retains the ability to form inclusion complexes, but is devoid of any significant toxicity.<sup>5,6</sup>

This study aims to improve the solubility and dissolution rate of NCDP through complexation with HPCD. The characterization of the inclusion complex of NCPD-HPCD was also investigated using DSC and IR techniques.

## MATERIALS AND METHODS

### Materials

Nicardipine hydrochloride,  $C_{26}H_{29}N_3O_6HCl$ , FW 516.0 (Sigma Chemicals, St. Louis, MO, USA), and HPCD ( $[\alpha]^{25} = +127^\circ$ ,  $c = 1$ ,  $H_2O$ ) with avg. MS 0.8 (Aldrich Chemicals, Milwaukee, WI, USA) were used as received. All other chemicals were of analytical reagent grades.

### Phase-solubility Studies

The purity of NCPD was monitored by an HPLC method,<sup>10</sup> and no appreciable contaminants could be detected. Phase-solubility studies were carried out according to the method reported by Higuchi and Connors.<sup>11</sup> Excess amounts of NCDP were placed into separate 15-mL screw-capped vials, to which 5 mL of distilled water containing various concentrations of HPCD (0 - 0.0667 M) was added. The vials were sonicated in an ultrasonic bath (Branson 5210, Danbury, USA) for 30 min and placed in a rotator (Fargo Instrument, Taipei, Taiwan) at  $25.0 \pm 0.1^\circ C$  for 48 h at a 100-rpm rotating rate. An aliquot of solution was withdrawn and filtered through a 0.45- $\mu m$  Millipore filter. The concentration of NCDP in each solution was determined by UV spectrometry in triplicate at 235 nm with a Hitachi U-2000 spectrophotometer (Tokyo, Japan).

### Preparation of the Physical Mixture and Inclusion Complex

Exactly weighed (1:1 molar ratio) amounts of NCDP and HPCD were carefully ground and mixed in

a ceramic mortar to prepare the physical mixture. The inclusion complex was prepared by a freeze-drying method.<sup>12</sup> The equilibrium solutions obtained from the phase-solubility studies were lyophilized and further kept in a desiccator before use.

### Characterization of the Physical Mixture and Inclusion Complex

The DSC thermograms of NCDP, HPCD, the physical mixture (1:1 molar ratio), and the freeze-dried inclusion complex were recorded on a Seiko Instrument SSC 5000 thermal analyzer (Chiba, Japan) equipped with a DSC cell using nitrogen as the purging gas. Each sample was subjected to DSC at a scanning speed of  $10^\circ C/min$  from ambient temperature to  $280^\circ C$ . The IR spectra were measured using potassium bromide discs on a Bio-Rad Win IR spectrometer (Cambridge, MA, USA).

### Dissolution Rate Studies

In order to study the dissolution rates, the prepared constant-surface-area discs were placed in a rotating apparatus (Fargo Instrument) at  $25.0 \pm 0.1^\circ C$  with a 50-rpm rotating rate. The discs were made up according to the formulations listed in Table 1. The 200 mg of accurately weighted NCDP powder was pulverized and mixed well in a ceramic mortar and then compressed under  $500\text{ kg/cm}^2$  pressure. Each disc was placed into a 15-mL screw-capped vial which contained 10 mL of 0.02 M phosphate buffer (pH 2.5). An aliquot of 0.50 mL solution was removed at each pre-determined checkpoint, and then 0.50 mL phos-

**Table 1. Formulations of NCDP Discs Containing Different Proportions of HPCD for Dissolution Studies<sup>a</sup>**

| Formulation     | NCDP | HPCD | Talc<br>(lubricant) | HPC <sup>b</sup><br>(binder) | Lactose<br>(diluent) |
|-----------------|------|------|---------------------|------------------------------|----------------------|
| Intact NCDP     | 1.5  | 0    | 1.5                 | 1.0                          | 96.0                 |
| 1:1 molar ratio | 1.5  | 8.5  | 1.5                 | 1.0                          | 87.5                 |
| 1:2 molar ratio | 1.5  | 16.5 | 1.5                 | 1.0                          | 79.5                 |
| 1:3 molar ratio | 1.5  | 25.0 | 1.5                 | 1.0                          | 71.0                 |

<sup>a</sup>All units expressed in %.

<sup>b</sup>HPC: hydroxypropyl cellulose.