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The Effect of Eudragit and Enteric Polymer Composite on the Release of Nicardipine

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ABSTRACT

The purpose of this study was to investigate the sustained release of nicardipine/polymer solid dispersions prepared by solvent evaporation method. The release pattern of drug from solid dispersions was evaluated by the dissolution test in both dissolution medium of phosphate buffer pH 6.8 or gastric acid fluid pH 1.2, and was compared with a commercial long acting product Perdipine®. The results showed that the formulations with lower ratio of Nicardipine/Eudragit RS (N/RS) (below 1/5) had sustained release effect in gastric acid fluid (pH 1.2). The release rate of formulation of N/RS = 1/5 was slightly faster than that of Perdipine® in gastric acid fluid in the early stage. On the contrary, the release rate was lower than that of Perdipine® in phosphate buffer (pH 6.8). The enteric polymers such as HPMCAS-LF grade (HPMCAS) and hydroxypropyl methylcellulose phthalate, HP-55 grade (HPMCP) were incorporated into the formulation of NC/ERS = 1/5 solid dispersion to improve the drug release in both dissolution medium. It was found that the dissolution efficiencies of drug were increased 2.35-21.08 folds with the addition of 20-40% of enteric polymer in pH 6.8 media. Among these formulations of N/RS/HPMCP = 1/3.5/1.5 had similar dissolution pattern with Perdipine® in either medium of phosphate buffer or gastric acid fluid (f_2 values were above 50), showing that the sustained release dosage form of nicardipine solid dispersions could be developed by using the combination of Eudragit RS and enteric polymer.

Key words: Nicardipine, Eudragit, Enteric polymer, Dissolution test

INTRODUCTION

Nicardipine (N), a dihydropyridine calcium channel antagonist, causes coronary and peripheral vasodilatation by blocking the influx of extracellular calcium across cell membranes. It has been reported that the action of nicardipine was arterioselective and effective for the treatment of hypertension, angina pectoris and cerebrovascular diseases[1-2]. Nicardipine has an extensive hepatic first-pass metabolism[3-4] following oral administration with systemic bioavailability ranging from 20 to 33%. Because of its short biological half-life (2-4 hr), the drug has to be given frequently (30 mg three times daily). Further, nicardipine has some side effects such as nausea, vomiting, flushing, headache, dyspepsia, anorexia and diarrhea, probably due to rapid absorption or gastric irritation[3-5]. Therefore, to attain a prolonged therapeutic effect and a reduced incidence of side effects, sustained release formulations of nicardipine such as alginate gel beads, tablets, granules and microspheres of nicardipine hydrochloride[6-9] have been developed to maintain a suitable plasma level for a long period of time, with minimal frequency of daily administration. It is known that nicardipine is a weak basic drug (pKa 7.2) which is easily solubilized in acidic solution rather than alkaline solution. It is difficult to prepare a sustained-release dosage form of a drug when its solubility is pH-dependent[10]. Several attempts to overcome the problem of pH-dependent solubility of weak basic drugs have been approached[11-18]. They are mostly based on the presence of acidic excipients, such as water-soluble or -insoluble polymers or organic acids, which either increase the permeability of the drug delivery system by leaching out at higher pH values or create an acidic micro-environment inside the polymer matrices and thus keep the solubility of the drug at high level.

In this study, the water-insoluble polymers such as Eudragit RL (RL) and Eudragit RS (RS) were used as retardants to prepare the sustained release dosage form of nicardipine/polymer solid dispersion by solvent evaporation method. The enteric polymers such as hydroxypropyl methylcellulose acetate succinate, LF grade (HPMCAS) and hydroxypropyl methylcellulose phthalate, HP-55 grade (HPMCP) were incorporated into the drug/polymers solid dispersions to modify the release rate of drug. The effects of the sustained release of nicardipine from drug/Eudragit/enteric polymer solid dispersions were evaluated by the dissolution test and compared with a commercial long acting product (Perdipine®).

MATERIALS AND METHODS

I. *Materials*

The following reagents were used: nicardipine hydro-

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chloride, p-hydroxybenzoate-butyl ester (TCI, Japan), Eudragit RS, Eudragit RL (Rohm Pharm, Germany), hydroxypropyl methylcellulose acetate succinate, LF grade (HPMCAS), hydroxypropyl methylcellulose phthalate, HP-55 grade (HPMCP) (Shin Etsu, Japan). Perdipine® was purchased from Yamanouchi (Japan). All other chemicals and solvents were of analytical reagent grade.

II. *Preparation of Drug/Polymer Solid Dispersion*

Solid dispersions with differing weight fractions of nicardipine/Eudragit/enteric polymers (Table 1) were prepared by solvent evaporation. The drug and polymers were dissolved in 40 mL of ethanol, and then the solvent was evaporated off under reduced pressure at 40°C for 24 hr. The residual solid was pulverized and the 20-40 mesh fraction was used in this study.

III. *Differential Scanning Calorimetry*

The endothermic peak heights and peak areas from thermogram of drug, solid dispersion and polymers were determined and compared using a Perking-Elmer DSC 7 data handling system. Thermograms were recorded from 120 to 200°C at a heating rate of 10°C/min.

IV. *Fourier Transformation-Infrared (FTIR) Spectroscopy*

Infrared spectra of drug and drug solid dispersion were acquied using a Perkin Elmer, Spectrum GX FTIR spectrometer. The sample and potassium bromide at ratio of 1/10 (w/w) were previously ground. The potassium bromide disks were prepared by compressing the powders, under 50 mPa of force for 15 sec in a hydraulic press. Sixteen scans were carried at a resolution of 4 cm^{-1}, from 2000 to 370 cm^{-1}.

V. *X-ray Diffractometry*

The powder X-ray diffraction patterns were determined using Model D5000 Siemems Diffractometer with a Cu-Kα anode and a graphite monochromator. The voltage and current were set at 40 Kv and 30 mA, respectively. The samples were analyzed in the 2θ angle range of 0-50° and the process parameters were set as: scan step size of 0.025° (2θ) and scan step time of 1.25 sec.

VI. *Drug Release Test*

Dissolution tests were performed in 900 mL of aqueous solution including gastric acid fluid pH 1.2 or phosphate buffer pH 6.8 by the paddle method with a rotation speed of 50 rpm at 37 ± 0.5°C. At fixed time intervals, the concentration of dissolved drug was automatically monitored UV absorbance at 240 nm. All dissolution experiments were carried out in sextuple.

VI. *Data Analysis*

The dissolution efficiency (DE) was defined as from the area under the dissolution curve at time t by the trapezoidal method.

The different release kinetics might reflect different release mechanisms. Therefore, three kinetic models including the zero-order release equation (Eq. 1), Higuchi equation (Eq. 2) and first-order equation (Eq. 3) were applied to process the *in vitro* data in order to find the equation with the best fit[19-20].

Table 1. Compositions of the experimental formulations (ratio)

Formulae	Nicardipine	Eudragit RL	Eudragit RS	HPMCAS	HPMCP
N/RL = 1/1	1	1			
N/RL = 1/2	1	2			
N/RL = 1/3	1	3			
N/RL = 1/5	1	5			
N/RS = 1/1	1		1		
N/RS = 1/2	1		2		
N/RS = 1/3	1		3		
N/RS = 1/5	1		5		
N/RS = 1/6	1		6		
N/RS/HPMCSA = 1/4/1	1		4	1	
N/RS/HPMCP = 1/3/2	1		3	2	
N/RS/HPMCP = 1/4/1	1		4		1
N/RS/HPMCP = 1/3.75/1.25	1		3.75		1.25
N/RS/HPMCP = 1/3.5/1.5	1		3.5		1.5
N/RS/HPMCP = 1/3/2	1		3		2

$Q = k_1 t$ (Eq. 1)

$Q = k_2 (t)^{0.5}$ (Eq. 2)

$\ln (Q) = k_3 t$ (Eq. 3)

where Q is the release percentage at time t. The k_1, k_2 and k_3 are the rate constants of zero-order, Higuchi and first order model, respectively.

In addition, the similarity factor f_2 is defined by the following equation and is used to compare the difference of dissolution profiles between the commercial product and experimental formulation[21].

$$f_2 = 50 \times \log\{[1 + (1/n)\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} \times 100\}$$

Where n is the number of sampling times, and *Rt* and *Tt* are the individual percentages dissolved at each time point, t, for the reference and test dissolution profiles, respectively. A f_2 values of 50 or greater (50-100) ensures the sameness or equivalence of the two curves and, thus, the performance of the two products.

RESULTS AND DISCUSSION

I. *Drug Release Test*

The dissolution time courses of nicardipine from various ratios of drug/Eudragit solid dispersions into gastric acid fluid pH 1.2 are shown in Figure 1. It can be seen that the dissolution rates of drug were increased as the ratio of drug/polymer increased from 1/5 to 1/1. Regarding the type of polymer, the release rate of drug from Eudragit RL solid dispersions (Figure 1A) was greater than that of from Eudragit RS solid dispersions (Figure 1B). The results could be explained by considering the chemical structure of Eudragit. The Eudragit RL and RS are synthesized from acrylic and methacrylic esters with high and low content of quaternary ammonium groups (0.2 and 0.1), respectively, thus making up solid dispersions with different water permeability[22-24]. In comparison of these dissolution patterns of experimental formulations to Perdipine®, the Eudragit RL solid dispersions almost did not have a sustained effect and the Eudragit RS solid dispersions had significant retardant effect while the ratio of drug/polymer was below 1/5. The release rate of formulation of N/RS = 1/6 was slower than Perdipine® in the period of 6 hrs. Among these formulation, the dissolution pattern of formulation of N/RS = 1/5 was close to that of Perdipine® most.

Because nicardipine is a weak basic drug, the solubility is pH-dependent[10]. The effect of altering the pH value of dissolution medium was evaluated. As expected, the release rate of both Perdipine® and N/RS = 1/5 in phosphate buffer pH 6.8 were remarkably than that in gastric acid fluid, pH 1.2, which mimics the *in vivo* absorption (Figure 2). By examing the dissolution patterns of N/RS = 1/5 and Perdipine® in either phosphate buffer or gastric acid fluid for simulating the *in vivo* absorption, it was found that in gastric acid fluid, the dissolution rate of N/RS = 1/5 was slightly higher than that of Perdipine®. On the contrary, in phosphate buffer, the release rate of drug from N/RS = 1/5 was lower than Perdipine®. The result might be attributed to the Perdipine® formulation components, which includes macrogol, polyoxyethylene sorbitan fatty acid ester and the capsule body containing sodium laurylsulfate as inactive ingredient[25]. Macrogol, polyoxyethylene sorbitan fatty acid ester and sodium laurylsulfate are surfactants which can enhance the solubility of drug in medium, thus increasing the dissolution rate. In this study, the Eudragit RS was chosen as retardant because it is water-insoluble and its water permeability is pH independent. Hence, in order to increase the drug release rate in pH 6.8 medium and decrease the release rate in pH 1.2 medium, various amounts of enteric polymers such as HPMCAS and HPMCP which dissolved in alkaline solution were added into the experimental formulations. The dissolution efficiencies of 300 min (ED300)

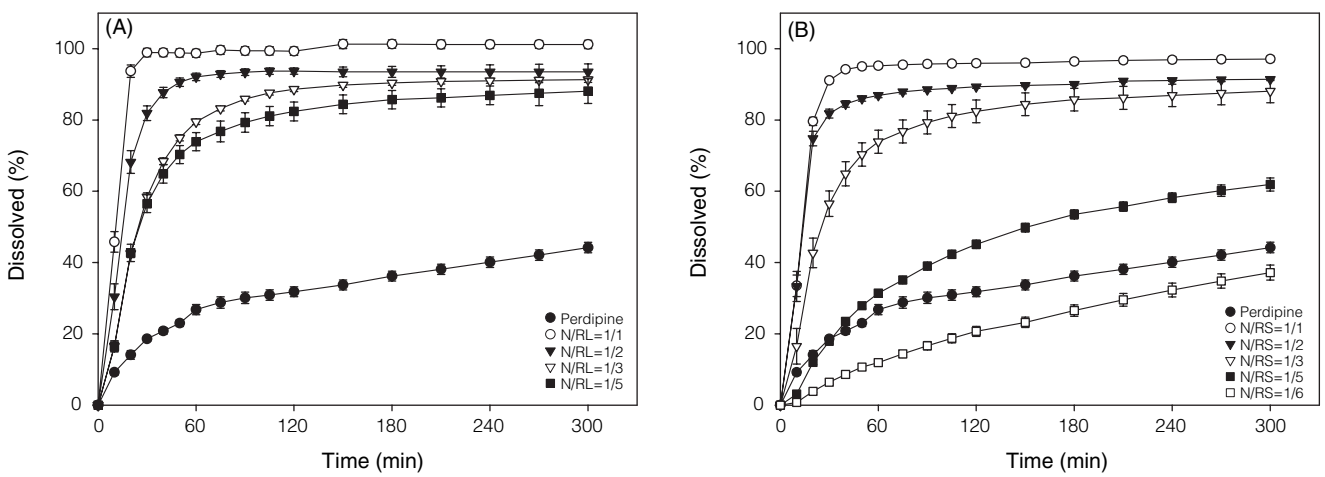

Figure 1. Dissolution profiles of nicardipine from drug/Eudragit solid dispersions and commercial product (Perdipine) in gastric acid fluid pH 1.2. (A for Eudragit RL; B for Eudragit RS).

were calculated from the area under the dissolution curve[26] and the results are listed in Table 2. Addition of 20-40% of enteric polymers could boost the dissolution efficiencies and dissolution rate up to 2.35-21.08 folds and 2.64-14.12 folds, respectively, indicating that these enteric polymer could significantly improve drug release

Table 2. Dissolution efficiency at 300 min (DE300) and release mechanism of correlation coefficients of nicardipine from Eudragit RS/ enteric polymer solid dispersions in phosphate buffer pH 6.8.

Formulae	Enteric polymer (%)		DE_{300}	IR (DE_{300})	Rate	IR (rate)	Zero-order (r^2)	Higuchi (r^2)	First-order (r^2)
N/RS = 1/5			518.00 ± 243.09	1	0.25 ± 0.08	1	0.9805	0.9858	0.8274
N/RS/HPMCSA = 1/4/1	HPMCAS	20	1989.11 ± 301.90	3.84	1.10 ± 0.20	4.40	0.9922	0.9782	0.8631
N/RS/HPMCAS = 1/3/2	HPMCAS	40	3351.03 ± 526.73	6.47	1.26 ± 0.14	5.04	0.8246	0.9119	0.6528
N/RS/HPMCP = 1/4/1	HPMCP	20	1215.25 ± 130.75	2.35	0.66 ± 0.08	2.64	0.9538	0.9916	0.8564
N/RS/HPMCP = 1/3.75/1.25	HPMCP	25	2494.31 ± 280.39	4.81	1.37 ± 0.10	5.48	0.9908	0.9933	0.8162
N/RS/HPMCP = 1/3.5/1.5	HPMCP	30	5726.12 ± 682.82	11.05	1.99 ± 0.03	7.96	0.9065	0.9663	0.8058
N/RS/HPMCP = 1/3/2	HPMCP	40	10919.80 ± 971.95	21.08	3.53 ± 0.16	14.12	0.9070	0.9679	0.7245

r: correlation coefficient
IR: increment ratio of dissolution efficiency

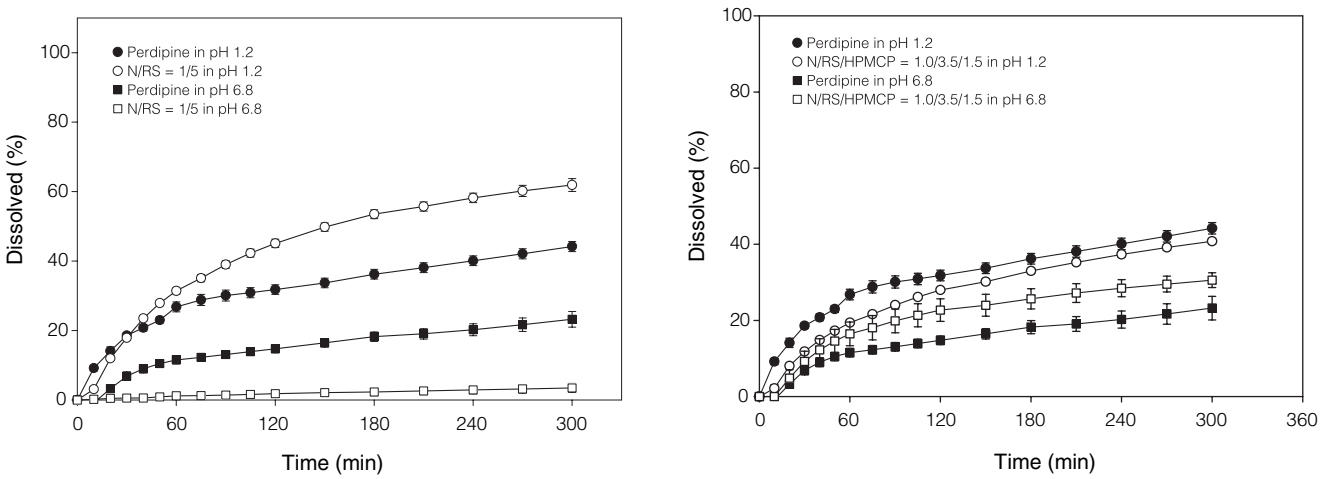

Figure 2. Dissolution profiles of nicardipine experimental formulations (N/RS = 1/5; N/RS/HPMCP = 1/3.5/1.5) and commercial product (Perdipine®) in gastric acid fluid pH 1.2 and phosphate buffer pH 6.8

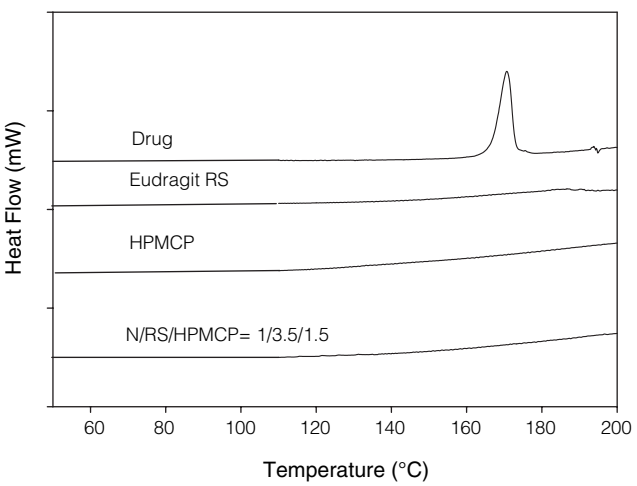

Figure 3. DSC thermograms of nicardipine hydrochloride, Eudragit RS (RS), HPMCAS and N/RS/HPMCP (1/3.5/1.5) solid dispersions. (Drug 0.5 mg).

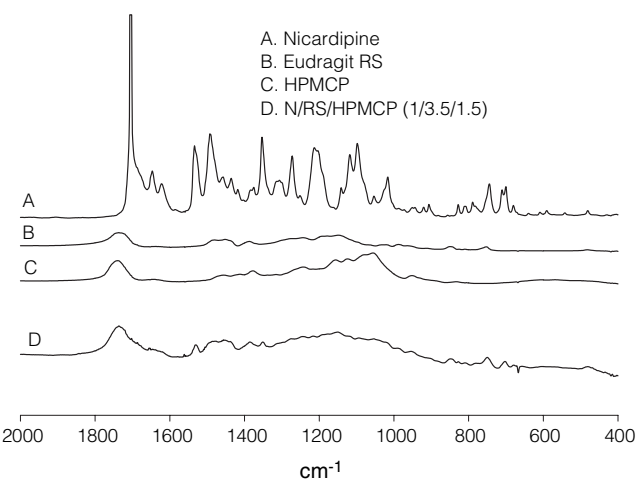

Figure 4. FTIR spectra (in absorbance) of nicardipine hydrochloride, Eudragit RS (RS), HPMCP and N/RS/HPMCP (1.0/3.5/1.5) solid dispersions.

in phosphate buffer. Moreover, the increment ratio of drug release from solid dispersion was increased with the increase in additional amounts of enteric polymers. Furthermore, it can be seen that HPMCP had a better increment effect than HPMCAS. The results were consistent with previous studies[11-12,15,18] which pointed that the enteric polymers can dissolve at higher pH value, and thus act as pore-formers to compensate the reduction of drug solubility. In comparison of the dissolution curves of experimental formulations with Perdipine®, the f_2 value between N/RS/HPMCP = 1/3.5/1.5 and Perdipine® were 57.19 in gastric acid fluid pH 1.2 and 61.97 in phosphate buffer, respectively, demonstrating the closeness of the two curves and, thus, the performance of the two products. In addition, the release mechanisms of nicardipine from these solid dispersions were evaluated on the basis of theoretical dissolution equations including zero-order, Higuchi equation and first order kinetic model[19]. As shown in Table 2, the release pattern of nicardipine from Eudragit solid dispersions corresponded best with Higuchi equation and diffusion model, and the enteric polymer did not change the release mechanism. Similar release kinetic model was also observed in Perdipine® (Higuchi model, $r^2 > 0.975$).

II. *Physical Characterizes*

The thermograms of pure compounds and corresponding binary system of drug/mixture polymer (1/5) are presented in Figure 3 (the other data not shown). The DSC trace of nicardipine was typical of a crystalline anhydrous substance, exhibiting a sharp endothermic peak at 174.4°C, corresponding to the melting point of the drug. The complete disappearance of the nicardipine endothermic peak was observed for the various ratios of drug/Eudragit/enteric polymer solid dispersions, indicating that there were strong interaction among nicardipine, Eudragit and enteric polymers in the solid state and formation of amorphous solid dispersions. From the FTIR spectroscopy in Figure 4, it was found that a strong absorption peak of carbony stretching vibration of nicardipine at 1703 cm^{-1} and some weak absorption peak were broader and shifted to lower wavenumber, suggesting the formation of hydrogen bonds between the carbonyl groups of nicardipine and hydroxyl groups of HPMCP[5,27]. The X-ray diffractograms of nicardipine, polymer and nicardipine dispersion were shown in Figure 5. It was found that the crystalline peaks of nicardipine disappeared, showing the entirely amorphous nature of nicardipine in the solid dispersions.

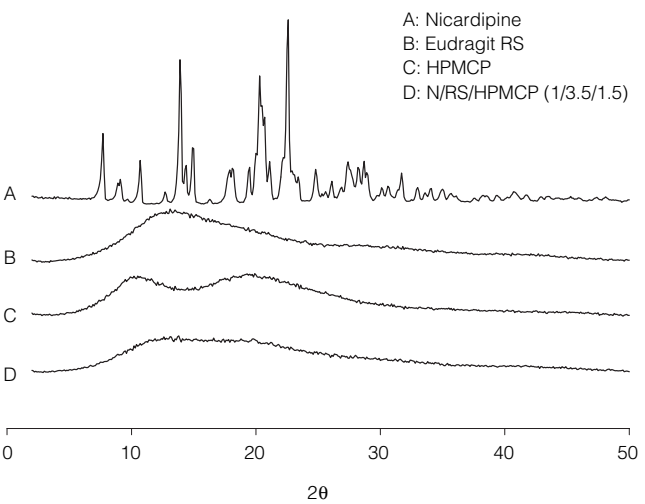

Figure 5. X-ray diffractograms of nicardipine hydrochloride, Eudragit RS (RS), HPMCP and N/RS/HPMCP (1.0/3.5/1.5) solid dispersions.

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