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Nifedipine Molecular Dispersion in Microparticles of Ammonio Methacrylate Copolymer and Ethylcellulose Binary Blends for Controlled Drug Delivery: Effect of Matrix Composition

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ABSTRACT The objective of this study is to explore matrix-type microparticles, comprising a solid dispersion of drug with an ammonio methacrylate copolymer and ethylcellulose binary blend, for use in the controlled release of a poorly water-soluble drug, nifedipine. Microparticles consisting of an ethylcellulose N7 (N7) and Eudragit RL® (RL) binary blend at different ratios were prepared using phase-separation methodology. The effects of matrix composition on microparticle properties were evaluated by polarized light microscopy, differential scanning calorimetry (DSC), FT-infrared and UV-visible spectroscopy, stability, and drug release studies. Study results indicate that the particle size distribution, particle morphology, and drug release rate from the microparticles were influenced by the ratio of RL to N7. Discrete spherical microparticles with a narrow size distribution and a controlled release profile were obtained when the ratio of RL to N7 was in the range from 1:1 to 2:1 w/w. Solid-state characterization and release kinetic studies on these microparticles confirmed that the nifedipine release from the microparticles followed the Baker and Lonsdale's matrix diffusion model (1974) for microspheres containing dissolved drug, and the nifedipine diffusion in the microparticle matrix was the rate-limiting step. As the ratio of RL to N7 was changed from 0:1 to 4:1 w/w, the effective drug diffusion coefficient in the micro-matrix increased from 5.8×10^{-10} to 8.6×10^{-9} (cm^2/h). In addition, probably due to formation of a stable molecular dispersion promoted by hydrogen bonding between nifedipine and the polymers, no significant changes in the nifedipine physical form or release kinetics were observed after 1-year storage at ambient room temperature followed by 3-month accelerated stability at 40°C/75% RH in a closed container.

KEYWORDS Nifedipine, Controlled release, Microparticles, Ethylcellulose, Ammonio methacrylate copolymer, Poorly water-soluble drug, Solid dispersion

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INTRODUCTION

Nifedipine (Fig. 1A) is a potent antianginal drug belonging to the class of calcium channel antagonists (Ali, 1989). However, due to a short clearance half-life in vivo, nifedipine immediate-release dosage forms need to be administered three times per day (Pfizer, 2003). Consequently, this dosing regimen results in a significant fluctuation in plasma drug concentration that causes side effects. Therefore, it is desirable to develop nifedipine controlled-release dosage forms to reduce side effects and to improve patient compliance. Currently, two nifedipine extended-released dosage forms containing the micronized drug particles are commercially available. Procardia XL® by Pfizer is a two-layer push-pull osmotic pump system containing an active drug layer and an osmotic agent layer as the internal core and a semipermeable membrane as the external surrounding materials (Pfizer, 2003).

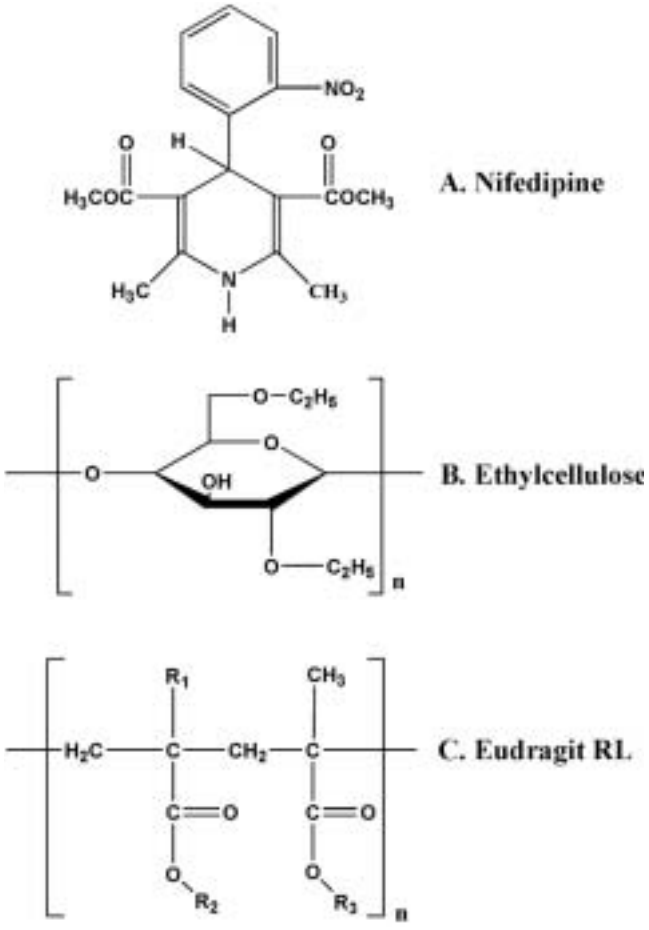

FIGURE 1 Molecular Structure of Nifedipine (A), Ethylcellulose (B). and Eudragit RL(C). R_1=CH_3, H; R_2=CH_3, CH_2CH_3; R_3=CH_2 $CH_2N^+(CH_3)_4Cl^-$; R_2:R_3 ≅ 3:0.2 mol/mol.

Whereas, Adalat CC® by Bayer is a coated tablet containing the core as an immediate release formulation and the coat as a slow release formulation (Bayer, 2004). In the literature, a variety of nifedipine oral solid dosage forms, such as nifedipine nanoparticles (Kim et al., 1997) and microspheres (Barkai et al., 1990; Benita et al., 1990) prepared by the emulsion solvent evaporation method, sandwiched osmotic tablets (Liu et al., 2000), hydroxypropylmethyl cellulose (HPMC) tablets containing a solid dispersion of nifedipine in PEG 6000 (Leucuta, 1988), a nifedipine solid dispersion in a water-soluble polymer prepared using a co-grinding method (Sugimoto et al., 1998), and microcapsules of a nifedipine solid dispersion in hydroxypropylmethyl cellulose-microcrystalline cellulose blend (HPMC-MCC) (Chowdary & Sankar, 1997), have been previously reported. However, matrix-type microparticles, containing a solid dispersion of nifedipine with a polymer mixture prepared by a phase-separation (co-precipitation) method, have not been found in the literature.

For a poorly water-soluble drug such as nifedipine with aqueous solubility of 5.6 μg/mL at pH 7 (Ali, 1989), the drug dissolution from its stable crystalline form normally is the slowest step for drug absorption in the human gastrointestinal tract. This factor is often the cause of drug bioavailability problems (Benita et al., 1990). Therefore, different physico-chemical modifications, such as reduction of particle size (Kornblum & Hirschorn, 1970) and solid dispersion of drug with polymers (Sekiguchi & Obi, 1961; Chiou & Riegelman, 1969), are required to improve the drug dissolution rate before any controlled-release technology can be applied. As an oral multiparticulate disperse system, matrix-type microparticles/nanoparticles containing uniformly dispersed or dissolved drug is a good example of controlled-release dosage forms that potentially can improve drug bioavailability and drug delivery of poorly water-soluble drugs (Barkai et al., 1990; Benita et al., 1990; Jaeghere et al., 1996; Kim et al., 1997; Guyot & Fawaz, 1998). Not only does it have advantages in avoiding dose "dumping," reducing local irritation, minimizing erratic drug absorption, and achieving a more reproducible drug release rate, but also it may improve bioavailability and prolong constant plasma drug concentration (Kim et al., 1997). Dispersion/dissolution of a water-insoluble drug within a polymeric micro-matrix may dramatically increase the dissolution rate locally inside the

polymer matrix by reducing the particle size to a minimum level (Leuner & Dressman, 2000). Once the drug dissolution rate is improved, a controlled delivery of drug may be achieved by conventional methods, such as changing the polymer matrix permeability.

Based on this concept, matrix-type polymeric microparticles prepared using phase-separation methodology were explored for use in the controlled delivery of nifedipine for this study. Insoluble, pH-independent polymers, ethylcellulose (EC) in two viscosity grades (Fig. 1B), Eudragit® RL (RL) (Fig. 1C), or their various combinations were used to prepare microparticles. Both EC and RL polymers have been widely used in polymeric coating (Chang et al., 2003), microencapsulation (Barkai et al., 1990; Benita et al., 1990), granulation (Klinger et al., 1990), and extrusion spheronization (Varshosaz et al., 1997) to produce controlled-release dosage forms. EC polymer known for its hydrophobicity, low permeability, and toughness is frequently used in micro-encapsulation, whereas latex-like, hydrophilic RL polymer is used extensively in sustained-release coating formulations due to its flexibility and moderate permeability (Chang et al., 2003). Due to differences in the polymer physical properties, it is possible that different combinations of these two polymers could generate microparticles of varied morphology and drug release rates. Based on this hypothesis, the effects of matrix compositions on the physico-chemical properties of the microparticles were investigated in this study.

MATERIALS

Micronized crystalline nifedipine (stable polymorphism A) was purchased from Sigma (St. Louis, MO). Ethylcellulose (containing 48.0–49.5% w/w of ethoxyl groups) in two viscosity grades, N7 and N50 (viscosity is ~7 and ~50 cps at 5% w/w, respectively), were kindly provided by Hercules (Wilmington, DE). Ammonio methacrylate copolymers, NF, Eudragit RL100® (RL) granules (viscosity is ~3 cps at 12.5% w/w), were donated by Rohm America (Piscataway, NJ). Acetone and methanol were purchased from Sigma-Aldrich (St. Louis, MO). All other materials were at least of analytical grade. The photosensitivity of nifedipine requires storage and handling of the drug sample under yellow light (~589 nm).

METHODS

Microparticle Preparation

Matrix-type microparticles, containing a solid dispersion of nifedipine with polymers, were prepared using phase-separation methodology. Approximately 0.833 g of nifedipine (nifedipine: polymer blend = 1:9 w/w) was dissolved in a 50-mL acetone solution containing 7.5 g of ethylcellulose and Eudragit polymer binary blends. Under a constant stirring at 600 rpm, 100 mL of purified water (a nonsolvent) was added dropwise (1 mL/min) to the drug and polymer solution. In the course of the nonsolvent addition, the drug and polymers were co-precipitated to form microparticles. At the end of the compounding, the resulting microparticle suspension was vacuum-filtered with a Whatman No. 5 filter disk (pore size: 2.5 μm) and then vacuum-dried at room temperature for 72 h. The dried microparticles were protected from light and stored in a desiccator at room temperature until use.

Measurement of Nifedipine Concentration

To determine the nifedipine loading, an appropriate amount of microparticles was dissolved in methanol to obtain a theoretical nifedipine concentration of 20 mg/L. The drug concentration was then analyzed using a UV-visible spectrophotometer at 236 nm with a standard curve prepared using bracketed concentrations of nifedipine in a methanol solution. To determine nifedipine concentration in 0.5% (w/v) sodium dodecyl sulfate (SDS) aqueous solution for the dissolution study, the solution was measured without dilution at the same wavelength of 236 nm, and the drug concentration was calculated with a standard curve prepared using bracketed concentrations of nifedipine in an aqueous 0.5% SDS solution. No interference from the polymers or SDS on the nifedipine assay was found at 236 nm.

Microscopic Characterization

Microparticles were dispersed in mineral oil on a glass slide and covered with a cover glass. The microparticles were observed under an Olympus polarized light microscope equipped with a digital camera and

image analysis software (Image-Pro® Plus 4.5 software for Windows™, San Diego, CA). A field containing approximately 100–300 microparticles was randomly selected for size analysis. The equivalent spherical diameter of a microparticle (d_s) was calculated from the projection area of the microparticle by Eq. (1). The geometric mean (median) diameter, the 50% size, was used to express the median size of the postfiltered microparticles (Fonner et al., 1981). The size measurement was repeated with three to seven replicates.

$$Diameter = 2\sqrt{\frac{area}{\pi}} \quad (1)$$

Differential Scanning Calorimetry

Thermal analysis was conducted using a conventional differential scanning calorimeter (DSC) (Model: DSC 2910, TA Instruments Inc., New Castle, DE, USA). In an open aluminum pan under a 10 mL/min stream of nitrogen purge, samples of 2–5 mg were heated from room temperature to 200°C at a heating rate of 10°C/min. Universal Analysis (version 2.5) software was used for analysis.

FT-Infrared

The Fourier-transformed infrared (FTIR) spectra of samples were obtained using an FTIR spectrophotometer (Nicollet Magna 560; Nicolet Instrument, Madison WI, USA). Approximately 2 mg of each sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. Samples were scanned 64 times from 400 to 4000 cm^{-1}.

Dissolution Study

United States Pharmacopoeia (USP) dissolution apparatus II (paddle method) was used for the nifedipine microparticle release studies. Dissolution study was performed under sink conditions and the dissolution medium temperature was maintained at 37 ± 0.5°C. Microparticle sample equivalent to 20 mg of nifedipine (equal to 20% of nifedipine equilibrium solubility) was added into 1000 mL of de-ionized water containing 0.5% (w/v) SDS, the dissolution medium, with a stirring speed of 50 rpm. Periodically, a 5-mL solution sample was withdrawn from the dissolution medium, filtered with a 0.45-μm hydrophilic filter disk, and measured by at 236 nm. The filter used for this study was presaturated with a nifedipine solution. Each solution sample was replaced with 5 mL of 0.5% SDS aqueous solution after sampling. The dissolution test was done with two or three samples ($n = 2–3$).

RESULTS

Physical Properties of Microparticles

Preliminary studies indicated that combination of ethylcellulose of low molecular weight (N7 viscosity grade) with RL was necessary to obtain microparticles of desired size and morphology by the phase-separation method for this study. Use of ethylcellulose polymer alone generated irregular-shape microparticles with rugged surface (Fig. 2A) that had an extremely slow release rate, whereas the microparticles prepared from the RL polymer alone cannot be separated by the traditional filtration method due to the formation of a viscous suspension. For ethylcellulose of higher molecular weight (N50 viscosity grade), its combination with RL polymer only generated microparticles with an undefined oblong shape (Fig. 2F) and a non-uniform size distribution. Therefore, further studies were focused on the combination of RL with low molecular weight ethylcellulose (N7).

At a nifedipine loading of approximately 10% (w/w), microparticles of various matrix compositions were prepared by changing the weight ratio of RL to N7. The physical properties of the microparticles of different formulations are summarized in Table 1. Acceptable encapsulation efficiency (%) was obtained for all formulations in this series. The actual drug loading was in the range from 85% to 112% of a targeted drug loading of 10% (w/w). The particle size, shape, and size distribution of the microparticles changed as a function of the microparticle polymeric composition. As the ratio of RL to N7 increased from 1:2 to 2:1 w/w, the microparticles gradually changed from an oblong to a spherical shape (Fig. 2B, C–D); the median microparticle size decreased from 38 to 13 μm; and the particle size distribution changed from a non-uniform, broad polydisperse distribution to nearly a monodisperse distribution (Fig. 3). However, at a higher ratio of RL to N7 (RL/N7=4:1), a polydisperse distribution with two particle size populations was observed (Fig. 2E). This phenomenon probably was a

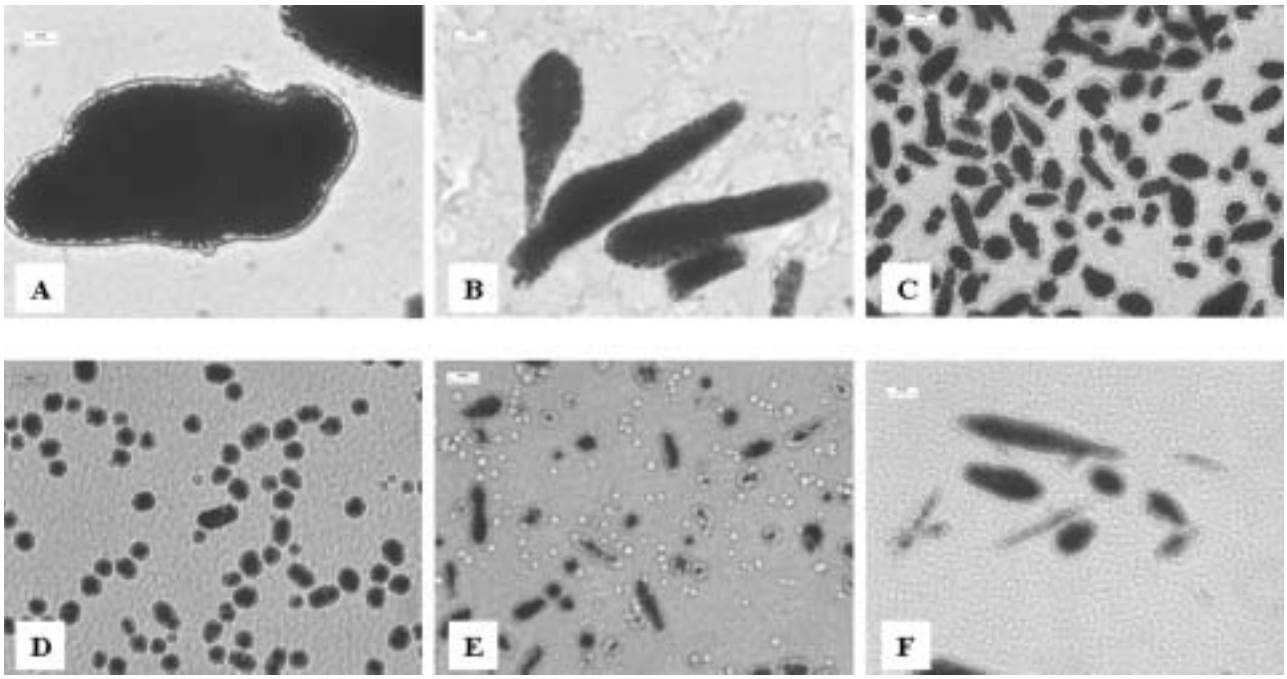

FIGURE 2 **Microscopic Photographs of Microparticles of Different Formulations (×40). The Scale Bars Represent 20 μm in Length. (A) Formulation 1: RL/N7 = 0:1; (B) Formulation 2: RL/N7 = 1:2; (C) Formulation 3: RL/N7 = 1:1; (D) Formulation 4: RL/N7 = 2:1; (E) Formulation 5: RL/N7 = 4:1; (F) Formulation 6: RL/N50 = 2:1.**

TABLE 1 **Physical Properties of Microparticles of Different Formulations at a Theoretical Nifedipine Loading of 10% (w/w)**

Formulation	Matrix composition RL/N7(50)(w/w)	Average median particle size (standard deviation) (μm)	Shape	Encapsulation efficiency[a] (%)
Formulation 1 (Nif:RL:N7=1:0:9)	0/1	112.1 (20.5)	Irregular	90
Formulation 2 (Nif:RL:N7=1:3:6)	1/2	38.4 (10.1)	Oblong	85
Formulation 3 (Nif:RL:N7=1:4.5:4.5)	1/1	18.7 (1.0)	Close to spherical	103
Formulation 4 (Nif:RL:N7=1:6:3)	2/1	13.3 (0.4)	Mostly spherical	110
Formulation 5 (Nif:RL:N7=1:7.2:1.8)	4/1	12.0 (2.0)	Oblong + spherical	112
Formulation 6 (Nif:RL:N50=1:6:3)	2/1	24.7 (7.6)	Oblong	101

[a]Encapsulation efficiency (%) = actual loading/theoretical loading × 100%.

result of the phase separation within the internal polymeric phase that produced RL-rich and N7-rich polymeric droplets (Sakellariou & Rowe, 1995).

Physical Form of Nifedipine in Microparticles

Considering the importance of the physical form of the drug to dosage form stability and drug release kinetics/mechanism, the physical forms of nifedipine in the microparticles were examined in this study. Previous study indicated that when the drug loading was below 21%, and 16% for the microparticles of formulations 2 (RL/N7=2:1) and 4 (RL/N7=1:2), nifedipine lost its x-ray crystallinity and was found being amorphously dispersed in the matrices (Huang et al., 2006).

The DSC thermograms (Fig. 4) and FTIR spectra (Fig. 5) of the representative formulations (formulations 2 and 4) further confirmed that the nifedipine was dissolved in the microparticles. A broad endothermic inflection together with ~1.3% of weigh loss at ~40–60°C, which was attributed to residual acetone evaporation (Sertsou et al., 2002), was observed on the

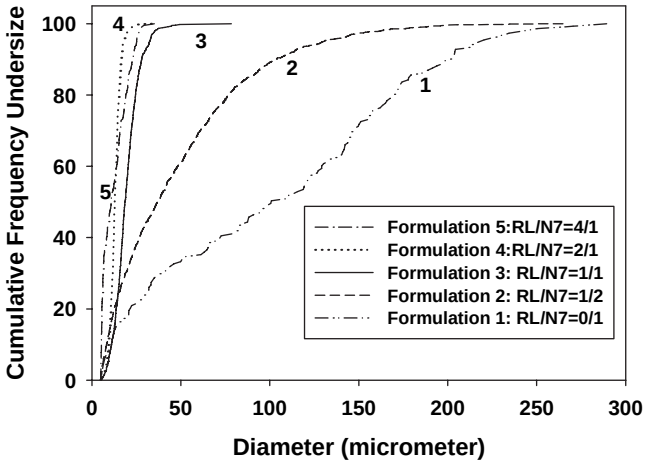

FIGURE 3 **Effect of the Ratio of RL to N7 on the Microparticle Size Distribution.**

microparticle samples. In addition, an exothermic ethylcellulose polymer degradation (Dubernet et al., 1991) at ~165°C was also observed in the DSC thermograms. Only one single glass transition, located at ~130°C and ~115°C, respectively, was detected for the nonloaded (placebo) and loaded microparticles. Neither the melting point of crystalline nifedipine of stable form nor the glass transition of amorphous nifedipine that was previously observed on the microparticles with higher levels of drug loading (Huang et al., 2006) was found in the DSC thermograms, suggesting that the drug was dissolved as stable molecular dispersion in the matrices of these two formulations. Moreover, when the FTIR spectra of formulations 2 and 4 (Fig. 5) were compared to that of pure crystalline nifedipine of stable form and the plain microparticles, the infrared stretching vibration of strongly hydrogen-bonded amine and carbonyl groups of crystalline nifedipine (self-associated between nifedipine amine and carbonyl groups) at 3332 cm^{-1}, 1679 cm^{-1}, and 1689 cm^{-1} disappeared in the spectra of these two formulations and were replaced by the stretching vibration of their weakly hydrogen-bonded forms formed between drug and polymers (3364 cm^{-1} for amine and 1706 cm^{-1} for carbonyl) (Huang et al.,

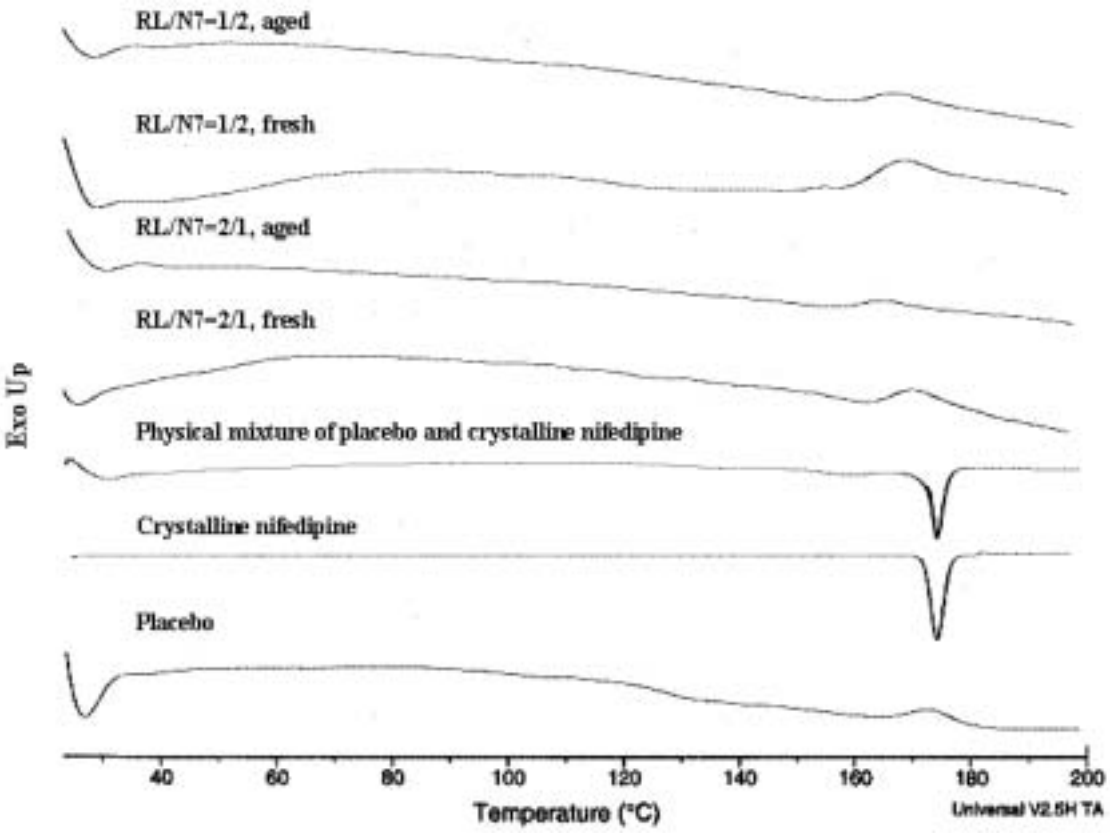

FIGURE 4 **Evaluation of Nifedipine Physical Form in Microparticles by DSC With a Scanning Rate of 10°C/min and a Nitrogen Purge. The Aged Microparticles Refer to the Stability Samples After 1-Year Storage at Room Temperature Followed by 3 Months at 40°C/75% RH in a Closed Container; Placebo Represents Plain Microparticles of RL/N7 = 2:1 (0% Drug Loading).**

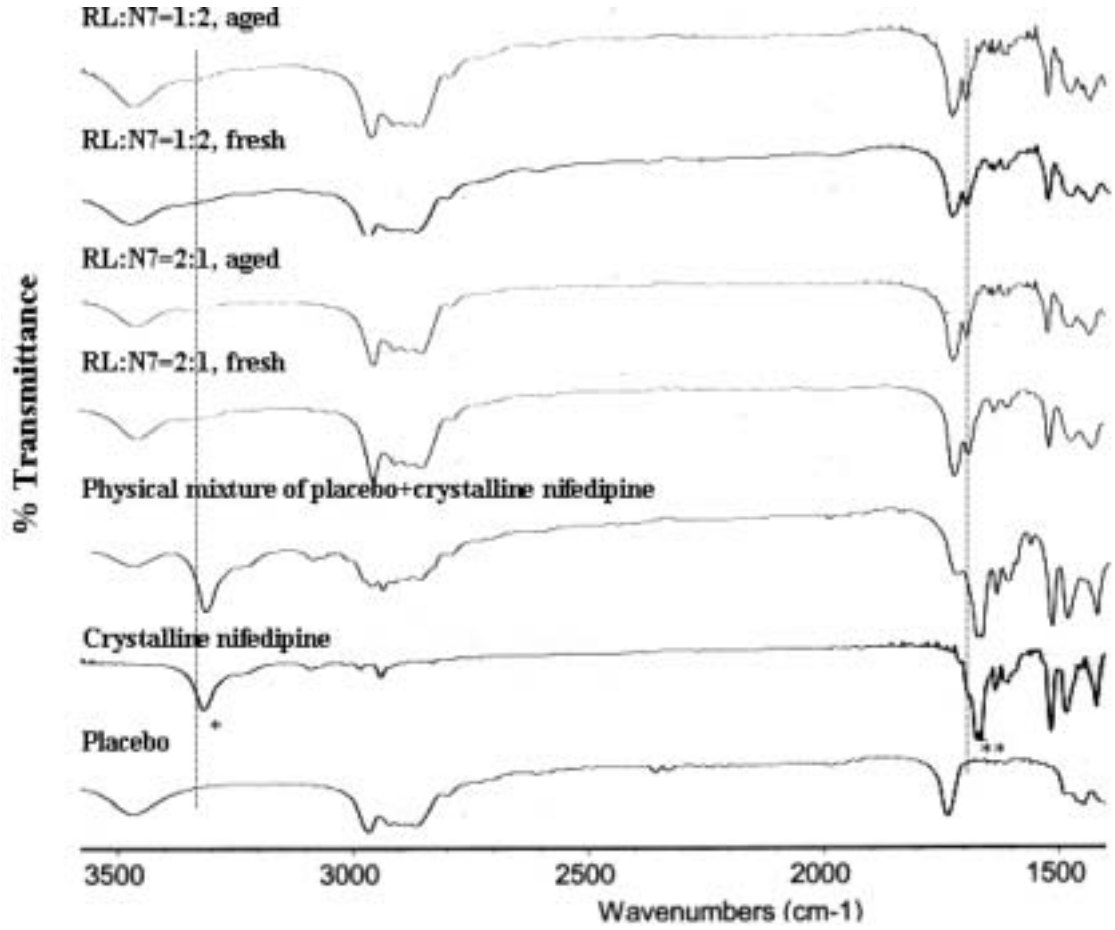

FIGURE 5 **Evaluation of Nifedipine Physical Form in Microparticles by FTIR. Dotted Vertical Lines Represent the IR Stretching Vibration of Nifedipine Amine (3364 cm^{-1}) and Carbonyl Groups (1706 cm^{-1}) Hydrogen-Bonded With Polymers, Respectively. The Aged Microparticles Refer to The Stability Samples After 1-Year Storage at Room Temperature Followed by 3 Months at 40°C/75% RH in a Closed Container; Placebo Represents Plain Microparticles of RL/N7 = 2:1 (0% Drug Loading); Nifedipine Crystalline Polymorph A Has Stretching Vibration at 3332 cm^{-1} for Amine Group (*) and 1679 and 1689 cm^{-1} for Carbonyl Group (**).**

2006). This phenomenon suggested that nifedipine was dissolved in the polymeric matrix, probably through the hydrogen-bond interactions between drug and polymers at the drug loading of 10% (w/w).

Drug Release Studies

The dissolution rates of nifedipine from the microparticles were found to be a function of the matrix composition. An improvement or retardation of the drug release rate, compared to that of micronized crystalline nifedipine, was achieved by changing the ratio of RL to N7 (Fig. 6A). The nifedipine release rate increased with an increase in RL fraction. When the ratio of RL to N7 was more than 1:1, the nifedipine release rate from the microparticles was higher than that from the crystalline form. To the contrary, when the ratio of RL to N7 was less than 1:1, the release rate was lower than that from the crystalline form. A similar effect of RL/EC polymer ratio on drug release rate was also observed on the microparticles prepared from the mixture of RL and ethylcellulose of a higher viscosity grade (N50). However, when the higher molecular weight ethylcellulose polymer was used, the nifedipine release rate from those microparticles became significant slower and was below that of crystalline nifedipine (Fig. 6B and C).

Stability of the Dosage Form

Recently, a solid dispersion technique has been used for the dissolution rate improvement of poorly water-soluble drugs. However, despite the advantages of solid dispersion described previously, the commercial

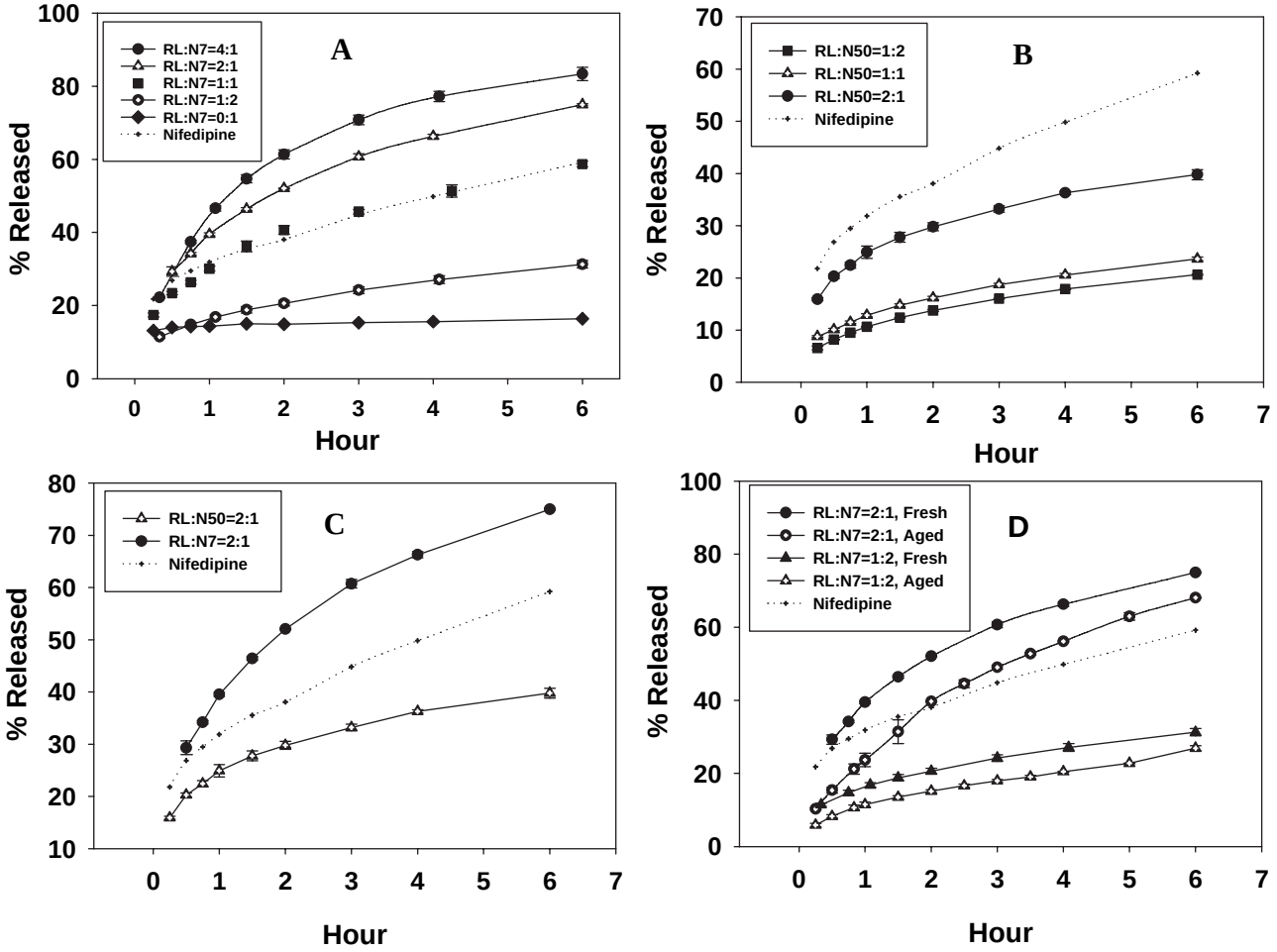

FIGURE 6 **Effect of Matrix Composition and Aging on the Nifedipine Release Rate From microparticles. Error bars indicate the Standard Deviation of 2–3 Replicates (n = 2–3); and Dotted Lines Represent the Drug Release From Micronized Crystalline Nifedipine. (A) Effect of the Ratio of RL to N7. (B) Effect of the Ratio of RL to N50. (C) Effect of Ethylcellulose Viscosity Grade. (D) Effect of Aging (1 Year at Room Temperature Followed by 3 Months at 40°C/75% RH).**

application of the solid dispersions dosage forms has been limited to a few commercial products (Serajuddin, 1999). Poor physical stability of the solid dispersion dosage forms was believed to be one of the major reasons responsible for this difficulty (Craig, 2002). To evaluate the physico-chemical stability of the microparticles for this study, microparticle samples of two representative formulations (formulations 2 and 4) were first stored in sealed amber containers and protected from light for 1 year in the ambient room temperature, and then they were placed in 40°C/75% RH chamber for an additional 3 months. Before and after the storage, the samples were examined for potency (drug loading), dissolution rate, and nifedipine physical form. Nifedipine assay results showed that no significant loss of nifedipine potency was seen after these storage conditions. The drug potency (% drug loading, w/w) of the freshly prepared and aged samples was found to be 8.5% (±0.042%) and 8.9% (±0.49%) for formulation 2 and to be 11.0% (±0.037%) and 11.6% (±0.40%) for formulation 4, respectively. No apparent changes in the infrared spectra and DSC thermograms of the aged microparticles from those of freshly prepared samples were observed for both formulations (Figs. 4 and 5). These are the indications that the drug physical form inside the microparticles did not change significantly after the storage conditions as described above. A slight decrease in the dissolution rate compared to that of freshly prepared samples was observed on both formulations of aged samples (Fig. 6D). However, the reduction in the released fraction at the 6-h release time point was no more than 7% of the total

drug loading. At this time point, the released fraction decreased from 31% to 27% for formulation 2 and from 75% to 68% for formulation 4.

DISCUSSION

Formation of Microparticles

The changes in the microparticle shape, particle size, and particle size distribution were most likely related to a change in the viscosity of the internal polymeric solution (Thomasin et al., 1998). Since the viscosity of the EC solution is higher than that of the RL solution, with a constant total polymeric concentration, the viscosity of the polymeric solution of EC/RL binary mixture decreased with increasing ratio of RL to EC. Because the emulsified droplets of a polymeric solution with a lower viscosity have less resistance to distortion caused by the shear force, the internal polymeric phase with a lower viscosity would tend to be fragmented into smaller emulsified droplets, which in turn solidified into microparticles of a smaller particle size. Another factor that may also play a role in determining the physical properties of the microparticles is the interfacial properties of the emulsified droplets (Thomasin et al., 1998). Polymeric droplets with a higher ratio of RL to EC contain more positive charged quaternary ammonium groups. The increases in the surface charge and the hydrophilicity of the polymeric droplets consequently extended the stability window of the polymeric droplets. As a result, the agglomeration and deformation of droplets were reduced due to a stronger electrostatic repelling force.

Mechanism of Release Rate Improvement

According to Nixon (1983), three steps lead to drug release from microparticles into the aqueous medium: (1) penetration of the dissolution medium (water) into the microparticles; (2) dissolution of the drug substance inside the microparticles; (3) drug release by a diffusion process into the aqueous medium. Under sink conditions, the slowest step described above would be the rate-limiting step for drug release from the microparticles into the aqueous medium. As previously known, microparticles prepared by a phase-separation method are hardened by solvent diffusion process outward into the external phase (Thomasin, et al., 1998). Therefore, the inward penetration of smaller water molecules into the micro-matrix should be rapid compared to the other two steps (Jalsenjak, 1992). For poorly water-soluble drugs such as nifedipine, the drug dissolution from its crystalline form was reported being the rate-limiting step for its release in human gastrointestinal tract, which often is the cause of bioavailability problem for oral dosage forms (Barkai et al., 1990; Benita et al., 1990). Nifedipine molecules in crystalline form must overcome the high crystalline lattice bond energy before it can dissolve into the dissolution medium. However, the molecular solid dispersion of nifedipine in the microparticle polymers may change the nifedipine release kinetics by altering the potential rate-limiting step. Molecular dispersions of nifedipine in polymer(s) may overcome the strong intermolecular lattice bond between nifedipine molecules and replace it with a weaker bond between drug and polymer. This may result in a dramatic improvement of the drug dissolution rate locally within the polymer matrix (Leuner & Dressman, 2000). Consequently, the dissolution of nifedipine would be no longer the rate-limiting step. Instead, the diffusion process of drug through the matrix can become the rate-controlling step by judicious selection of the polymers. Eventually, the nifedipine release rate into the dissolution medium could be simply controlled by diffusion of the drug through the matrix, or, more simply, matrix permeability. For this study, DSC and FTIR confirmed that nifedipine was molecularly dispersed in the micromatrices through hydrogen-bond interactions between drug and polymers. The improvement and retardation of the nifedipine release rate resulting from changes in the ratio of RL to N7 support the hypothesis of this study. Specifically, a change in nifedipine physical form resulted in a system where the dissolution rate of nifedipine was no longer the rate-limiting step, but rather the release kinetics was controlled by drug diffusion within the microparticle matrix.

Effects of Formulation and Stability on Drug Release

The release mechanism of dissolved nifedipine from microparticles was previously investigated (Huang et al., 2006), demonstrating that drug release

from microparticles with dissolved nifedipine was best described by the Baker and Lonsdale's matrix-diffusion model for microspheres containing dissolved drug (Baker & Lonsdale, 1974). Since the current study indicates that nifedipine was dissolved in the micromatrices at a drug loading of 10% (w/w), the Baker and Lonsdale's release model was used for data analysis. The original Baker and Lonsdale's equations are listed below as Eqs. (2, 3), assuming that no surface free drug is present.

For short time, valid for $M_t/M_\infty < 0.4$

$$\frac{M_t}{M_\infty} = 6\left[\frac{D^* t}{r^2 \pi}\right]^{1/2} - \frac{3D^* t}{r^2} \tag{2}$$

For long time, valid for $M_t/M_\infty > 0.6$

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left[\frac{-\pi^2 D^* t}{r^2}\right] \tag{3}$$

where M_t and M_∞ are the amount of drug released at time t and the total drug loading; D, r, and t are the effective drug diffusion coefficient, radius of the microparticles, and time unit for release, respectively.

Considering the possibility of free drug present at the periphery of microparticles, which would be available for immediate release, the original equations were modified to add a new term, F_o, representing the fraction of surface free drug available for burst release (Eqs. [4, 5]).

For short time periods, when $6\left[\frac{D^* t}{r^2 \pi}\right]^{1/2} - \frac{3D^* t}{r^2} < 0.4$

$$\frac{M_t}{M_\infty} = F_0 + (1 - F_0)\left\{6\left[\frac{D^* t}{r^2 \pi}\right]^{1/2} - \frac{3D^* t}{r^2}\right\} \tag{4}$$

For long time periods, when $1 - \frac{6}{\pi^2}\exp\left[\frac{-\pi^2 D^* t}{r^2}\right] > 0.6$

$$\begin{aligned}\frac{M_t}{M_\infty} &= F_0 + (1 - F_0)\left\{1 - \frac{6}{\pi^2}\exp\left[\frac{-\pi^2 D^* t}{r^2}\right]\right\} \\ &= 1 - (1 - F_0)\left\{\frac{6}{\pi^2}\exp\left[\frac{-\pi^2 D^* t}{r^2}\right]\right\}\end{aligned} \tag{5}$$

where M_t/M_∞ is the fraction of released drug at time t, including the entire surface free drug immediately released at time zero and the drug released from the inside of the microparticles at time t; D, r, and t were previously defined.

Since the release studies on these different formulations suggested a minimal drug burst release, Eqs. (4, 5) were further simplified to Eqs. (6, 7), assuming $F_0 \ll 1$.

For short time periods, when $M_t/M_\infty < F_o + 0.4(1 - F_o) \cong F_0 + 0.4$

$$\frac{M_t}{M_\infty} = F_0 + 6\left[\frac{D^* t}{r^2 \pi}\right]^{1/2} - \frac{3D^* t}{r^2} \tag{6}$$

For long time periods, when $M_t/M_\infty > F_o + 0.6(1 - F_o) \cong \quad F_0 + 0.6$

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left[\frac{-\pi^2 D^* t}{r^2}\right] \tag{7}$$

where M_t/M_∞, D, r, t were defined previously.

Nonlinear regression of the release data using Eqs. (6, 7) indicate a high level of correlation between the nifedipine release data from the microparticles and the Baker and Lonsdale's model (Table 2). Based on Eqs. (6, 7), the effect of the ratio of RL to N7 on the drug release rate was analyzed by two major factors: particle size ($1/r^2$) and diffusion coefficient (D). First, studies showed that the microparticle particle size became smaller when the ratio of RL to N7 was increased (Table 1). Therefore, the increase in the release rate was in part due to the particles size reduction that caused a decrease in the drug diffusion path length. Second, since there is approximately 6% of molar substitution by the positive charged quaternary ammonium functional group (Lehman, 1996), RL is more permeable than N7. Different combinations of RL and N7 should generate microparticles of varied permeability that would affect drug diffusion coefficient accordingly. To evaluate this variable independently, drug release was normalized with respect to particle size by plotting the released drug fraction against t/r^2 (time/radius^2) (Fig. 7). The effective drug diffusion coefficient (D) and the fraction of surface free drug (F_o) for different formulations were obtained by nonlinear regression of the normalized release data using

TABLE 2 **Parameters Derived from Nonlinear Regression With Baker and Lonsdale's Matrix Diffusion Model for Microspheres Containing Dissolved Drug (Eqs. [6, 7])**

Formulation	Matrix composition RL(RS)/N7(50) (w/w)	Effective Drug Diffusion Coefficient, D (SE) ($\times 10^{-8}$ cm^2/hr)	Free drug fraction, F_0 (% w/w)[a]	Regression R Square, r^2
Formulation 1 (Nif:RL:N7=1:0:9)	0/1	0.058 (0.011)	12.9	0.9474
Formulation 2 (Nif:RL:N7=1:3:6)	1/2	0.41 (0.008)	5.0	0.9997
Formulation 3 (Nif:RL:N7=1:4.5:4.5)	1/1	0.49 (0.015)	5.8	0.9989
Formulation 4 (Nif:RL:N7=1:6:3)	2/1	0.64 (0.008)	2.4	0.9994
Formulation 5 (Nif:RL:N7=1:7.2:1.8)	4/1	0.86 (0.028)	–4.0	0.9970
Formulation 6 (Nif:RL:N50=1:6:3)	2/1	0.28 (0.026)	10.0	0.9923
Formulation 2, aged (Nif:RL:N7=1:3:6)	1/2	0.31 (0.009)	0.6	0.9993
Formulation 4, aged (Nif:RL:N7=1:6:3)	2/1	0.47 (0.011)	–7.5	0.9997

[a]Negative values indicate a lag time in drug release.

Eqs. (6, 7) (Table 2). As expected, the normalized release profiles indicated that an increase in RL/N7 polymer ratio caused an upward trend in normalized release rate. As the ratio of RL to N7 was increased, the matrix permeability expressed by the effective drug diffusion coefficient increased. Further analysis on the changes of D and $1/r^2$ as a function of matrix polymer composition indicated that $1/r^2$ was more sensitive to a change in RL/EC polymer ratio than D. An increase in the RL/N7 ratio resulted in a greater change in $1/r^2$ than D (Fig. 8). Therefore, even though changes in RL/N7 ratio affected both D and $1/r^2$, the size ($1/r^2$) change appeared to have a bigger impact in modifying drug release rate than that of drug diffusion coefficient. For the microparticles prepared from ethylcellulose of higher viscosity grade (formulation 6), the reduction of nifedipine diffusion coefficient compared to formulation 4 was attributed to an increase in the matrix tortuosity or a reduction in the free void volume of polymer network for drug diffusion (Table 2) (Fan & Singh, 1989).

For the aged microparticles, the drug release kinetics were the same as that of the freshly prepared microparticles. The Baker and Lonsdale's matrix diffusion model for microspheres containing dissolved drug is still valid. However, as indicated by a reduction in drug diffusion coefficient (Table 2), a decrease in matrix permeability was observed for the aged stability samples of formulations 2 and 4. Since no significant changes in the drug potency and physical form were detected by chemical assay, DSC, and FTIR, the

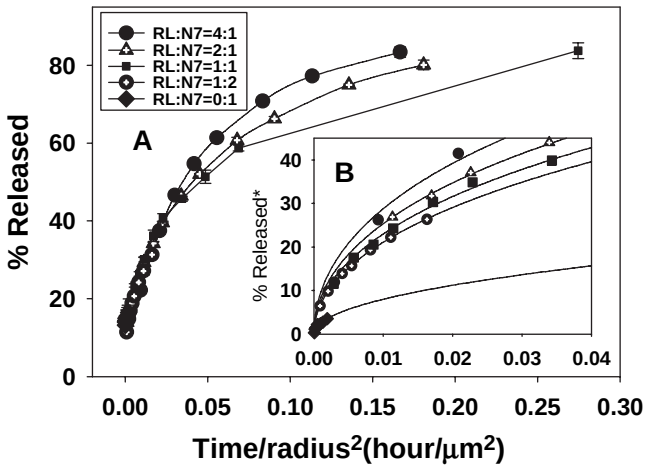

FIGURE 7 **Evaluation of the Effect of RL/N7 Ratio on Normalized Release Rate With Respect to Microparticle Size. (A) Effect of the Ratio of RL to N7. (B) Enlarged View of Normalized Drug Release Profiles; Solid Lines in B Represent the Prediction of Normalized Drug Release Rate by Eqs. (6, 7). * For Comparison and a Clear View of Trend in Drug Release Rate, the % Released of Y-Axis in B Represents the Fraction of Released Drug Corrected by the Surface Free Drug as Determined by Eqs. (6, 7).**

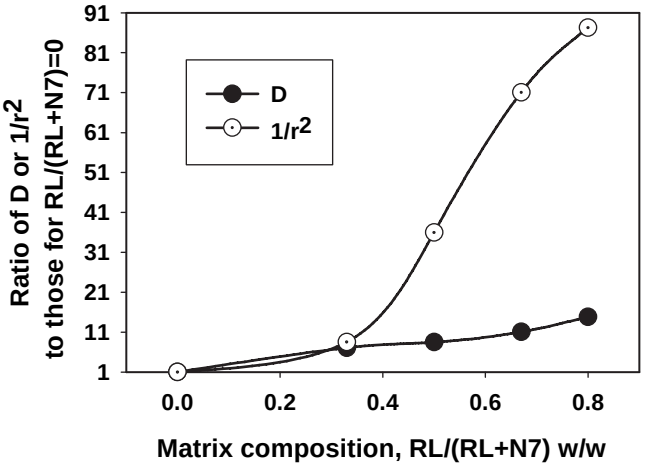

FIGURE 8 **Comparison of the Effects of Matrix Composition on Microparticle Size ($1/r^2$) and Diffusion Coefficient (D).**

decrease in the drug diffusion coefficient may suggest a change in polymer permeability due to rearrangement of polymer network (Sinko et al., 1990; Guo et al., 1991; Lovrecich et al., 1996) during the stability study. Because glassy polymers at its metastable high energy state were not in thermodynamic equilibrium below their glass transition temperature, those polymers would undergo a slow process called "physical aging" to a more stable state at a temperature lower than its glass transition point, rearranging its polymeric structure and thus decreasing its free volume within the network (McCrum, et al., 1988). As a result, the decrease in the free volume of the polymer network caused a corresponding decrease in the solute mobility inside the polymer (or the polymer permeability) (Guo et al., 1991). Moreover, since the physical aging process is a function of temperature relative to its glass transition point, the presence of residual solvent/water, which acted as a plasticizer lowering the glass transition temperature of the matrix polymers, may even accelerate this rearrangement process.

CONCLUSIONS

Microparticles containing a nifedipine molecular solid dispersion with desired micromeritic properties and varied matrix permeability can be prepared from ethylcellulose and Eudragit RL polymer blends using the phase-separation method. The improvement or retardation of drug release rate, compared to that of micronized crystalline nifedipine, resulting from changes in the ratio of RL to N7, demonstrated the feasibility of this formulation strategy for controlled delivery of nifedipine. And last, microparticles containing a molecular dispersion of nifedipine in an ethylcellulose N7 and Eudragit RL polymer blend with a RL/N7 ratio in the range from 2:1 to 1:2 were physico-chemically stable after 1-year storage at ambient room temperature followed by 3-month accelerated stability at 40°C/75% RH in a closed container, likely due to formation of a stable molecular dispersion promoted by hydrogen bonding between drug and polymers,

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