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RESEARCH PAPER

Multi-unit Controlled Release Systems of Nifedipine and Nifedipine:Pluronic® F-68 Solid Dispersions: Characterization of Release Mechanisms

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ABSTRACT

Nifedipine (N) and nifedipine : Pluronic® F-68 solid dispersion (SD) pellets were developed and characterized for drug release mechanisms from a multi-unit erosion matrix system for controlled release. Nifedipine was micronized using a jet mill. Solid dispersion with Pluronic F-68 was prepared by the fusion method. Nifedipine and SD were characterized by particle size analysis, solubility, differential scanning calorimetry (DSC), and x-ray diffraction (XRD) studies. Samples were subsequently processed into matrix pellets by extrusion/spheronization using Eudragit® L 100-55 and Eudragit® S 100 as release rate-controlling polymers. Drug release mechanisms from pellets were characterized by microscopy and mercury intrusion porosimetry; DSC and XRD studies indicated no polymorphic changes in N after micronization and also confirmed the formation of SD of N with Pluronic F-68. Pellets of N showed a 24-hr drug release profile following zero-order kinetics. Pellets of SD showed a 12-hr release profile following first-order kinetics. Aqueous solubility of N after SD formation was found to be increased 10-fold. Due to increased solubility of N in SD, the drug release

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mechanism from the multi-unit erosion matrix changed from pure surface erosion to an erosion/diffusion mechanism, thereby altering the release rate and kinetics.
Key Words: *Eudragit® L 100-55; Eudragit® S 100; Extrusion/spheronization; Nifedipine; Pluronic® F-68; Porosity; Solid dispersions*

INTRODUCTION

Nifedipine is a poorly water-soluble drug and when administered orally in the crystalline form has poor bioavailability. For poorly soluble drugs, dissolution is the rate-limiting step for gastrointestinal absorption of the drug from solid dosage forms. Since dissolution rate is directly proportional to surface area, a decreased particle size may increase the dissolution rate. Numerous attempts have been made to modify the dissolution characteristics of drugs to attain more rapid and complete absorption (1–5).

Controlled release Oros® tablets of nifedipine are commercially available. The drug from such an Oros tablet releases in the form of a microfine suspension through a laser-drilled hole in the tablet via osmosis following zero-order kinetics for 24 hr. Osmotic controlled release multi-unit pellets and granules of nifedipine have also been reported (6). The mechanism of polymer controlled surface erosion that provides a constant delivery of a poorly soluble drug via multi-unit erosion matrix was reported in our previous study (7). In such a system the drug release was found to be proportional to matrix erosion. Hence, matrix erosion could be used to predict drug release. This system consisted of Eudragit® L 100-55 and Eudragit® S 100 which were used as matrix-forming and release rate-controlling polymers. These are anionic polymers based on methacrylic acid and methacrylic acid esters. The ratio of carboxyl groups to ester units is about 1 : 1 in Eudragit L 100-55 and about 1 : 2 in Eudragit S 100. These polymers are soluble above pH 5.5 and 7.0 respectively. The model drug (nifedipine), Eudragit, and polyvinylpyrrolidone (binder) were wet granulated and later pelletized using an extrusion/spheronization technique. The effects of dissolution stirring rate, polymer ratio, granulation water requirement, drug loading, pellet size, and spheronization time on the release patterns and porosity parameters were reported earlier (8).

Solid dispersions of poorly soluble drugs provide alternatives to increasing drug solubility and bioavailability. Law et al. (9) showed increased oral absorption and bioavailability of nifedipine–polyethylene glycol and nifedipine–phosphatidylcholine–polyethylene glycol solid dispersions in rats. Solid dispersions of nifedipine with different carriers such as urea, lactose, PEG 4000, 6000, 10,000, and PVP K-30, K-90 have been studied by Sumnu (10). However none of these solid dispersions were evaluated for their release patterns from the final controlled drug delivery system, and there are not many studies determining the influence of solid dispersions on drug release mechanisms via solid dosage forms.

Release mechanisms of a drug from solid dosage forms may be related to the porosity. Porosity is a result of the presence of voids and pores in a sample where voids are the inter-particulate spaces and pores are typically the crevices, cracks, and fissures located in the particle (11). Porosity can be characterized by mercury intrusion porosimetry. The pore structure of a solid can provide valuable information regarding its dissolution and diffusion properties (12). Therefore, porosity and pore size distribution measurements have been used extensively to study tablets (13–18), granules (19–23), and pharmaceutical powders (24,25). Void porosity can be characterized by low-pressure mercury porosimetry (up to 30 psi) and is determined by calculating the pore volume diameter. In contrast, pores are analyzed by high-pressure mercury porosimetry (up to 30,000 psi). According to this method, the cumulative volume of mercury intruded is a function of porosity; increased volumes indicate an increased porosity.

The present study was undertaken to develop, characterize, and evaluate the multi-unit erosion matrix as described previously (7) with nifedipine and nifedipine : Pluronic® F-68 solid dispersion. Physical characterization of nifedipine solid dispersion by particle size analysis, aqueous solubility, differential scanning calorimetry (DSC), and x-ray diffraction (XRD) studies were conducted before they were pelletized. Later, pellets containing nifedipine or nifedipine : Pluronic F-68 solid dispersions were prepared by an extrusion/spheronization

technique. The effect of porosity parameters (cumulative intrusion volume, pore size distribution, pore volume diameter, total intrusion volume, and total pore surface area) on dissolution time (8) of the pelletized nifedipine and nifedipine : Pluronic F-68 solid dispersion were determined to better explain the mechanism of drug release from controlled release matrix pellets, and to determine the differences that were introduced by the nifedipine : Pluronic F-68 solid dispersions.

MATERIALS AND METHODS

Materials

Nifedipine (USP/BP) was purchased from Vinchem, Inc. (Chatham, NJ) and was micronized using a Fluid Energy Aljet Mill (Plumsteadville, PA). Inlet air pressure of 60 psig and grinding air pressure of 80 psig for micronization were used. Also used were Eudragit L 100-55, Eudragit S 100 (Rohm Pharma Polymers Division, Degussa Corporation, Piscataway, NJ), Kollidon® 90 F (BASF, Inc., Parsipanny, NJ), Avicel® PH 101 (FMC Corporation, Philadelphia, PA), triethyl citrate (Morflex, Inc., Greensboro, NC), and Pluronic F-68 (BASF, Inc., Parsipanny, NJ). All other chemicals were used as received. Since nifedipine is light-sensitive, all experiments were performed under yellow light.

Methods

Particle Size Determination

Particle size determination was carried out with a Master Sizer X (Malvern Instruments, Inc., Southborough, MA). An excess amount of drug was suspended in 1.0% v/v Tween 80 in 100 mL of distilled water and sonicated for 30 sec for a thorough dispersion. This suspension was circulated at medium speed for particle size distribution studies.

Preparation of Nifedipine : Pluronic F-68 Solid Dispersions

Solid dispersions with different drug : Pluronic F-68 ratios were prepared by the fusion method (26). The required amount of Pluronic F-68 was weighed accurately and heated to 100°C until it formed a transparent melt. Nifedipine (mean particle size: 2.31 μm) was added to this melt in small portions with a constant stirring rate of 750 rpm. The temperature of the mixture was kept constant at 100°C. This mixture was stirred for 45 min until a clear transparent melt was formed. The melt was then poured onto a glass plate and allowed to solidify at room temperature. The solid mass was powdered and mixed uniformly in a mortar; 80/100 mesh (150–180 μm) particles were used for pelletization.

Solubility Determination of Nifedipine and Nifedipine in Pluronic F-68 Solid Dispersion

Solubility of nifedipine alone and nifedipine in the Pluronic F-68 solid dispersion (1 : 1) was determined by placing an excess amount of sample in amber glass vials with 10 mL deionized water. The samples were subsequently allowed to equilibrate at 25°C in an incubator shaker for 24 hr. Samples were filtered and the filtrate was analyzed for nifedipine by a high-performance liquid chromatography (HPLC) method. A Waters 600E multi-solvent delivery system (Waters Corporation, Milford, MA), connected to a variable wavelength absorbance detector (Model Spectra 100, Spectra-Physics, Mountain View, CA) and a Waters 717 plus autosampler (Waters Corporation, Milford, MA), was used. The stationary phase consisted of a micro-bondapak C_{18} reverse phase column ($3.9 \times 300\,mm^2$, Waters Corporation, Milford, MA). Mobile phase used was acetonitrile : methanol : distilled water (2 : 3 : 5) and the flow rate was 1.0 mL/min with 30 min of total run time per injection. Nifedipine was detected at a retention time of 15.8 min. The sensitivity of the assay was 1 μg/mL. All studies were performed in triplicate.

Differential Scanning Calorimetry and X-ray Diffraction Studies

Differential scanning calorimetry was carried out with a Seiko Instruments, Inc., Japan, Model SSC5200 system. Approximately 6–8 mg of sample was placed in a hermetically sealed aluminum pan and scanned at a rate of 10°C/min from 0 to 200°C. Qualitative powder x-ray diffraction was performed with a Scintag X-Ray Diffractometer System, CA using nickel-filtered copper potassium alpha radiation.

Preparation of Pellets

Eudragit L 100-55 and Eudragit S 100 were mixed in a Turbula mixer (Impandex, Inc., Maywood, NJ)

for 30 min. Triethyl citrate was added to this mixture as a plasticizer by trituration in a mortar. Nifedipine or nifedipine solid dispersion was then added followed by Kollidon 90 F used as a binder; they were mixed for 30 min in a Turbula mixer. The resultant mixture was granulated with deionized water in a mortar. The granulate obtained was then fed through an extruder (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Osaka, Japan), equipped with a single screw and a screen of 2.0 mm size. Extrusion was conducted at 40 rpm. Extrudates obtained were immediately processed into pellets by spheronization (Spheronizer Model 120, G.B. Caleva Ltd., Dorset, UK attached to a 2.0 mm cross-hatched friction plate). The spheronization speed was maintained within 800–1000 rpm and spheronization time was limited to 10 min. During this process Avicel PH 101 (5% w/w of total batch size) was sprinkled onto the pellets to prevent inter-pellet sticking. Pellets thus obtained were dried on trays in a hot air convection oven for 12 hr at 50°C. They were then sieved (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., Mentor, OH) to obtain 2.0 mm sieve fractions. The quantitative composition of the pellets formulated is given in Table 1.

Determination of In Vitro Drug Release

In vitro dissolution was performed using USP XXII Apparatus I in 500 mL of pH 6.8 phosphate buffer with ionic strength of 0.05 M, at 50 rpm and 37.0 ± 0.5°C using 100 mg of pellets in each basket (Distek, Inc., North Brunswick, NJ) as described by Mehta et al. (7). Pellets obtained after dissolution were characterized for their shape and structure by an optical microscope (Nikon HFX, East Rutherford, NJ). Transverse sections of pellets obtained after 2 and 4 hr dissolution time were analyzed for the distribution of drug in the matrix.

Determination of Porosity Parameters

Pellet dissolution time as a function of cumulative intrusion volume of mercury, pore size distribution, pore volume diameter, total intrusion volume, and total pore surface area was determined by mercury intrusion porosimetry. A Micromeritics PoreSizer Model 9320 (Micromeritics, Inc., Norcross, GA) was used for the determinations. Three tests per sample were conducted. A detailed description of the porosity parameters mentioned above was given earlier by Mehta et al. (8).

The pore diameter was calculated using Eq. (1):

$$D = \frac{-4\gamma \cos\theta}{P} \tag{1}$$

where:

D = pore diameter (μm),
γ = surface tension of mercury (485 dynes/cm),
θ = contact angle (130°),
P = pressure (psia).

Table 1

Composition of Pellets Prepared with Nifedipine and Nifedipine : Pluronic F-68 Solid Dispersions

Formulation Type	Nifedipine (% w/w)	Pluronic F-68 (% w/w)	Kollidon 90 F (%w/w)	Eudragit L 100-55 : S 100 (1 : 3 ratio) (% w/w)	Triethyl Citrate (% w/w Relative to Eudragit polymers)[a]
Nifedipine pellets $D(V, 50) = 7.06$ μm	20.00	—	2.00	78.00	15.00
Nifedipine pellets $D(V, 50) = 2.66$ μm	20.00	—	2.00	78.00	15.00
Nifedipine pellets $D(V, 50) = 2.31$ μm	20.00	—	2.00	78.00	15.00
Nifedipine : Pluronic F-68 SD pellets (1 : 1)	20.00	20.00	2.00	58.00	15.00
Nifedipine : Pluronic F-68 SD pellets (1 : 0.5)	20.00	10.00	2.00	68.00	15.00

[a]Plasticizer for Eudragit polymers.

The total pore surface area (S) was calculated using Eq. (2):

$$S = \frac{1}{\gamma \cos\theta} \int_0^{V_{tot}} P \, dV \quad (2)$$

where:

P = pressure (psia),
V = intruded volume of mercury (mL/g),
V_{tot} = total intruded volume of mercury (mL/g).

RESULTS AND DISCUSSION

Results of particle size determination are listed in Table 2. The solubility of nifedipine and nifedipine in the nifedipine : Pluronic F-68 (1 : 1) solid dispersion was found to be 9.72 ± 0.13 and 103.06 ± 0.07 μg/mL respectively, demonstrating that Pluronic F-68 increased the solubility of nifedipine approximately 10 times. It is beyond the scope of this work to investigate the exact mechanism by which this solubility enhancement occurred, it was only measured to study the effect of increased solubility of the poorly soluble drug nifedipine and its effect on the release mechanism from the multi-unit erosion matrix pellets.

Differential scanning calorimetry thermograms and XRD patterns of micronized nifedipine indicated no changes in its thermodynamic and crystalline behavior (Figs. 1a and 1b). Data obtained indicate that the crystalline nature of nifedipine remained the same after micronization. Figures 2a and 2b are the thermograms of nifedipine : Pluronic F-68 solid dispersions that were prepared in ratios of 1 : 0.5 w/w drug to polymer ($T_m = 167.8°C$, $\Delta H = 50.7$ mJ/mg) and 1 : 1 w/w ($T_m = 152.6°C$, $\Delta H = 24.2$ mJ/mg) respectively. From these thermograms it was clear that the melting point of nifedipine was reduced in the solid dispersion, with consequent reduction in enthalpy. Figures 3a and 3b are XRD patterns of nifedipine : Pluronic F-68 solid dispersions in ratios of 1 : 0.5 and 1 : 1 w/w respectively. The characteristic nifedipine peaks were found to reduce with increased concentration of Pluronic F-68 in the solid dispersion. These results provide evidence of decreased drug crystallinity due to the formation of a solid dispersion. Similar results were reported for nifedipine solid dispersions with

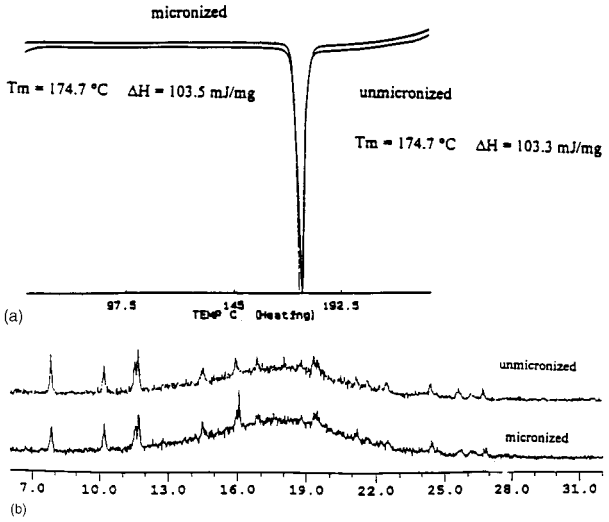

Figure 1. (a) Melting point endotherms and (b) x-ray diffraction pattern of nifedipine before and after micronization.

Table 2

Results of Particle Size of Nifedipine and Nifedipine in Pluronic F-68 Solid Dispersions

Sample	$D(V, 0.5)$ (μm)[a]	$D(V, 0.9)$ (μm)[b]
Nifedipine	7.06	17.29
Nifedipine micronized once	2.87	8.72
Nifedipine micronized twice	2.31	6.96
Nifedipine : Pluronic F-68 (1 : 1) SD	3.10	12.93
Nifedipine : Pluronic F-68 (1 : 0.5) SD	2.66	8.40

[a]50th Percentile mean volume particle size.
[b]90th Percentile volume particle size.

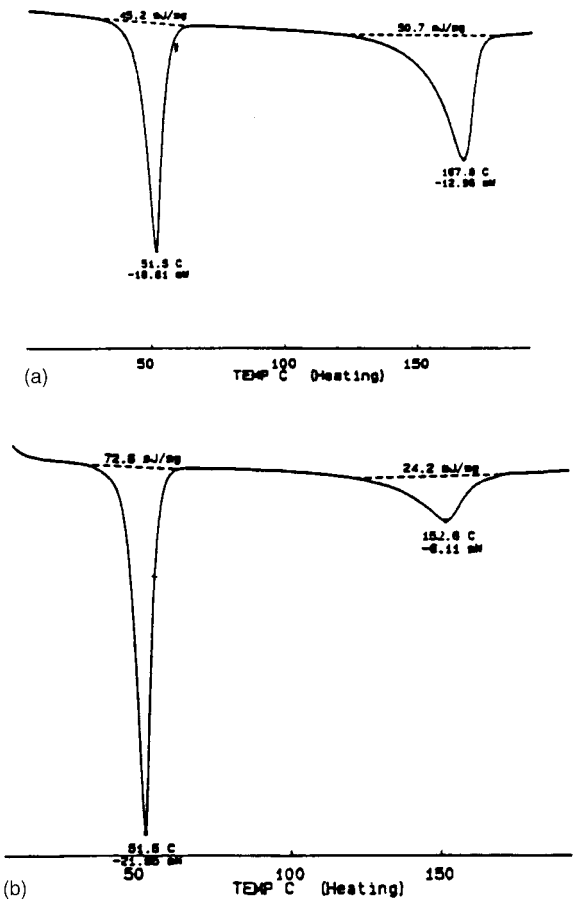

Figure 2. Melting point endotherms of nifedipine: Pluronic F-68 solid dispersions: (a) 1:0.5 and (b) 1:1.

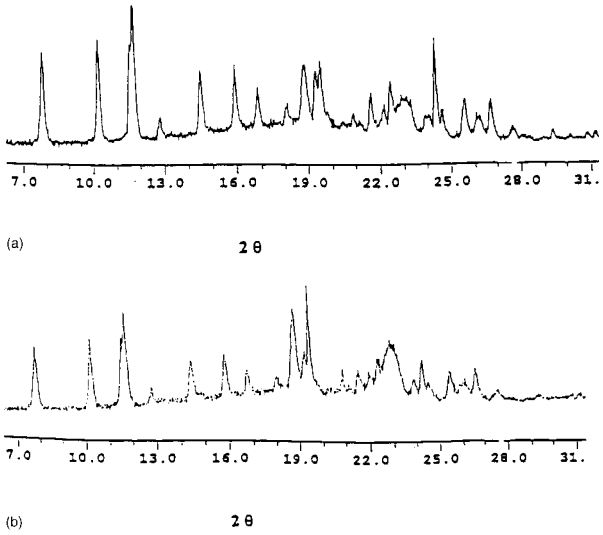

Figure 3. X-ray diffraction patterns of nifedipine: Pluronic F-68 solid dispersions: (a): 1:0.5 and (b) 1:1.

various other substances (9,10), such as polyethylene glycol, urea, lactose, polyvinylpyrrolidone, etc.

A linear relationship of drug release via matrix erosion of a poorly soluble drug, similar to nifedipine, was described in our earlier study (7). The validity of this matrix erosion hypothesis was tested with nifedipine and nifedipine: Pluronic F-68 solid dispersion pellets. The in vitro release profiles of nifedipine pellets before and after micronization and of nifedipine: Pluronic F-68 solid dispersion pellets are shown in Fig. 4. Pellets prepared with nifedipine of three different particle sizes provided a zero-order 24-hr drug release profile. On the other hand, drug release from the pellets prepared with nifedipine: Pluronic F-68 solid dispersions changed from zero to first-order, and the release rates increased significantly compared to the pellets prepared with nifedipine alone. Drug release rates from the solid dispersion pellets were increased as Pluronic F-68 increased from 0.5 to 1.0 parts in the solid dispersion. Dissolution from these pellets followed first-order kinetics for about 12 hr for both strengths. From Fig. 4 it can also be concluded that particle size differences of nifedipine did not significantly influence the release pattern and rates from nifedipine pellets.

In order to understand the underlying release mechanism, the pellets collected at different time intervals during dissolution testing were analyzed under the microscope. Figure 5 shows pellets prepared with nifedipine: Pluronic F-68 (1:1) solid dispersion after 12 hr of dissolution. The size of the pellets was decreased due to surface erosion. Nifedipine pellets also eroded in a similar fashion over a period of 24 hr. Both these pellets maintained their geometrical shape but were reduced in size. Furthermore, pellets of nifedipine and nifedipine: Pluronic F-68 (1:1) solid dispersion that were removed from the dissolution medium at 2 and 4 hr of dissolution time were dried at 50°C for 12 hr and transverse sections of these pellets were analyzed by microscopy. After 4 hr the pellets became very soft, which made it impossible to obtain the transverse section. Transverse sections of nifedipine pellets (Fig. 6a) showed that the drug remained uniformly distributed in the matrix at 2 and 4 hr, whereas

transverse sections of nifedipine : Pluronic F-68 (1 : 1) solid dispersion pellets (Fig. 6b) showed release of the drug from the core by diffusion. The increased aqueous solubility of drug in the solid dispersion explains the enhanced erosion and release rates from nifedipine : Pluronic F-68 solid dispersion pellets compared to nifedipine pellets. Increased aqueous solubility also increased the release of drug from the pellets of solid dispersion that occurred by erosion and simultaneous diffusion from the matrix. However, release of drug from nifedipine pellets was found to occur by an erosion mechanism.

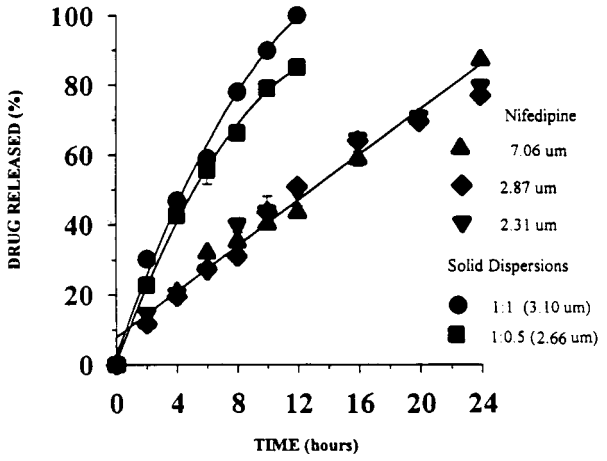

Figure 4. Effect of nifedipine mean particle size and ratio of nifedipine : Pluronic F-68 solid dispersion on the release profiles obtained with 2.0 mm pellets. (Spheronization time = 10 min, $n = 4 \pm SE$.)

To further confirm the release mechanisms of both the pellets, their porosity parameters were measured and determined by mercury intrusion porosimetry. The porosities were determined after the pellets were exposed to 2, 4, 6, and 8 hr of dissolution media. Figures 7a and 7b show the cumulative intrusion volume of mercury against pore diameters obtained at different dissolution intervals of nifedipine and nifedipine : Pluronic F-68 solid dispersion pellets, respectively. Figures 8a and 8b show changes in the pore size distribution during dissolution. Figure 7a shows that the cumulative intrusion volumes of mercury for nifedipine pellets following dissolution at 2–8 hr remain mainly constant, with minimal changes, whereas from Fig. 7b pellets of nifedipine : Pluronic F-68 solid dispersion showed increased pores as the dissolution time increased from 2 to 8 hr. Further, from Fig. 8a a trimodular pore size distribution is observed with maximum pores lying within the range 0.1–0.01 μm, indicating that the voids and fine pores contribute to the overall porosity of the pellets, with the pores occupying a much higher volume than the voids.

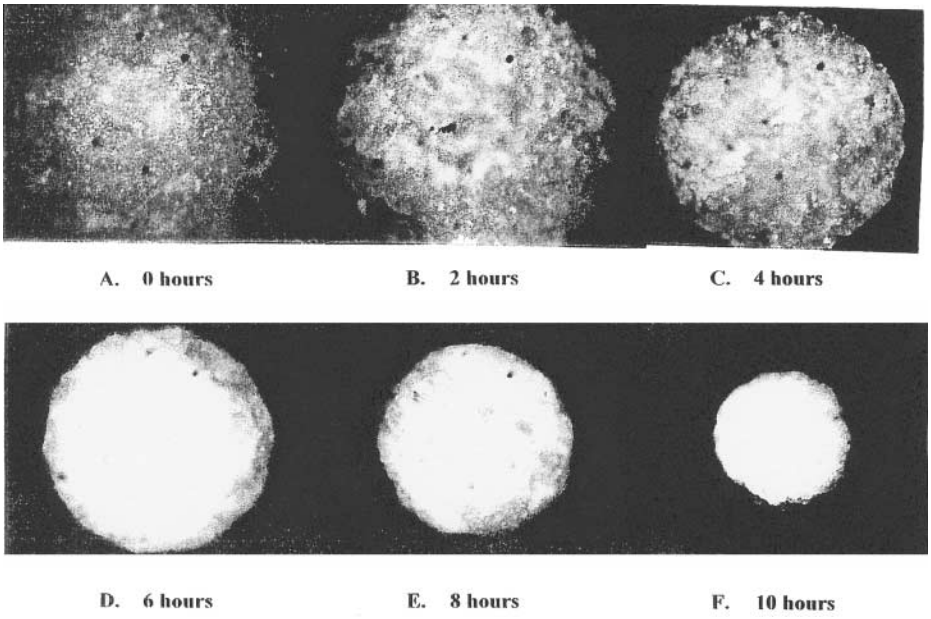

Figure 5. Microscopical evaluation of nifedipine : Pluronic F-68 (1:1) solid dispersion pellets after dissolution time intervals.

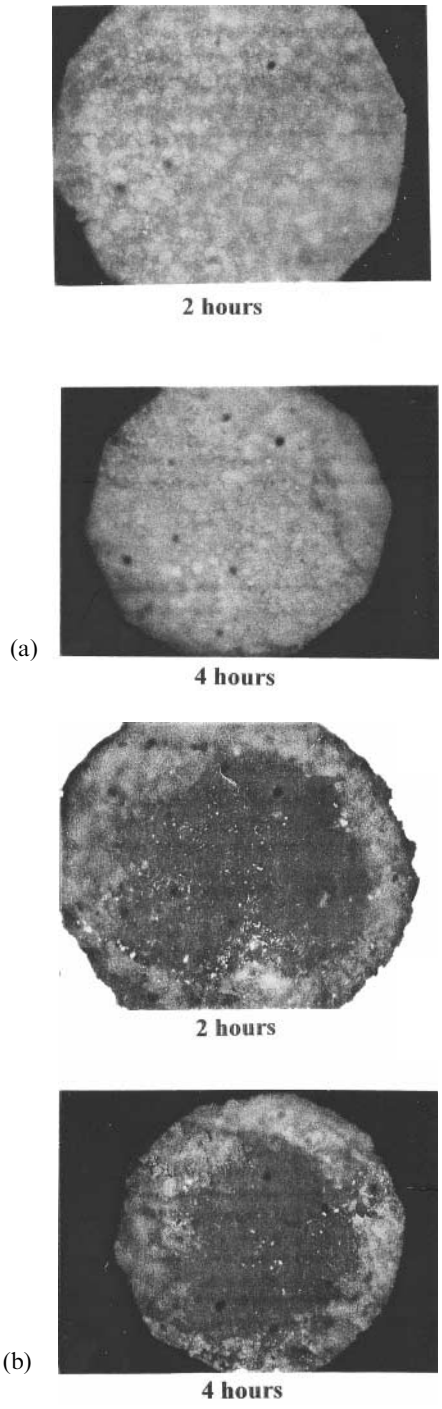

Figure 6. (a) Transverse section nifedipine pellets after 2- and 4-hr dissolution time intervals showing uniform drug distribution in the matrix. (b) Transverse section of nifedipine:Pluronic F-68 (1:1) solid dispersion pellets after 2- and 4-hr dissolution time intervals showing drug diffusion through the matrix.

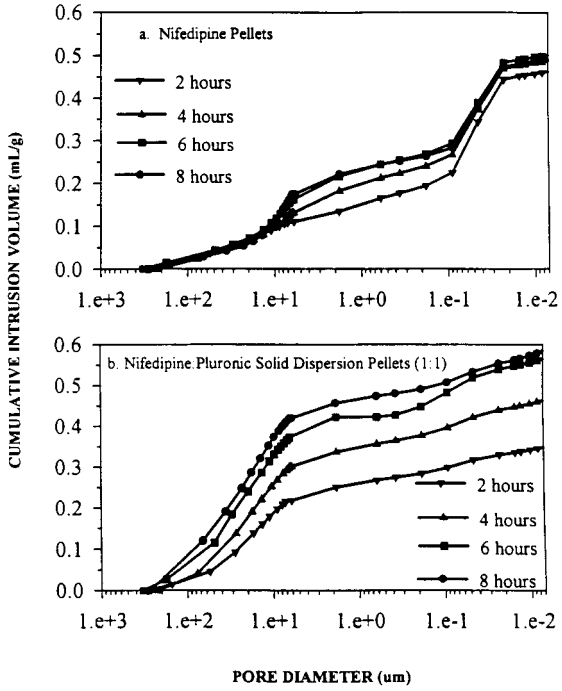

Figure 7. Cumulative intrusion profiles of nifedipine and nifedipine : Pluronic F-68 solid dispersion pellets during dissolution.

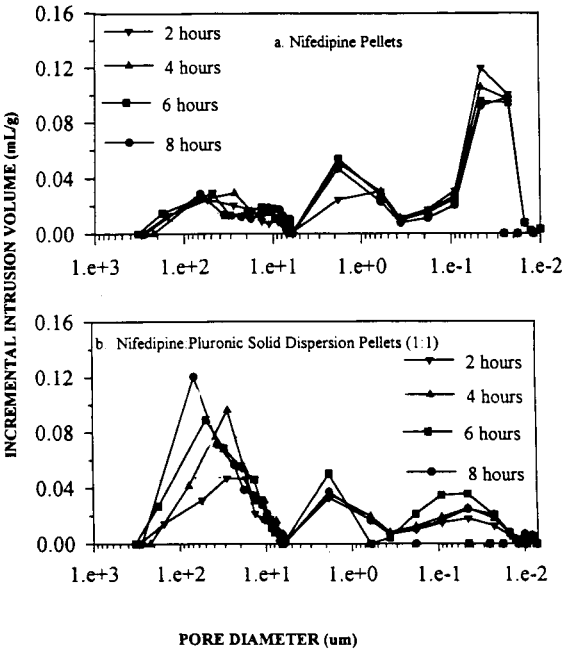

Figure 8. Pore size distribution of nifedipine and nifedipine : Pluronic F-68 solid dispersion pellets during dissolution. (Spheronization time = 10 min, $n = 4 \pm$ SE.)

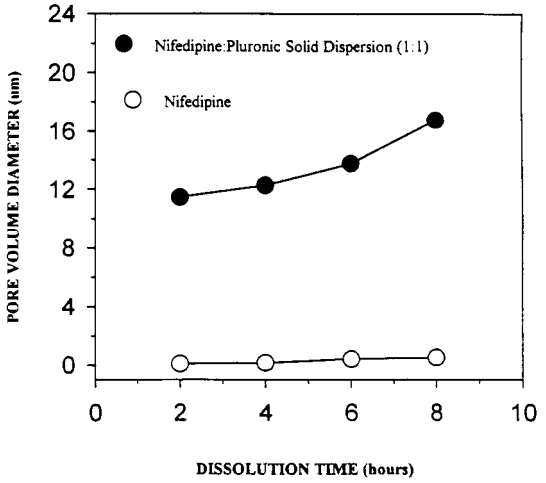

Figure 9. Changes in the pore volume diameter of pellets during dissolution.

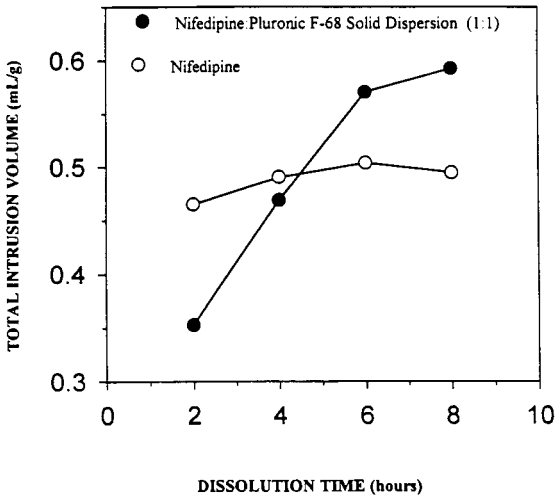

Figure 10. Changes in the total intrusion volume of pellets at various dissolution intervals.

A reverse pore size distribution was observed (Fig. 8b) for pellets of nifedipine : Pluronic F-68 (1 : 1) solid dispersion, indicating that the overall porosity was due to the voids which were increasing with dissolution time. Figure 9 shows the effect of dissolution time on the pore volume diameter of the pellets. No significant changes were observed in the pore volume diameters of nifedipine pellets, indicating no increase in void porosity during the dissolution period of 8 hr, whereas pore volume diameters of pellets formulated with nifedipine : Pluronic F-68 (1 : 1) solid dispersions increased with dissolution time, indicating an increase in the void porosity which is the result of increased void diameters. This increase may be due to the enhanced solubility of drug in the solid dispersion that diffused out of the matrix. Figure 10 shows the total intrusion volumes that were obtained at different dissolution times, summarizing the overall effect of dissolution time on pellet porosity. From this figure the porosity of nifedipine : Pluronic F-68 solid dispersion pellets increased linearly with dissolution time, whereas the porosity of nifedipine pellets did not change significantly. Total pore surface area is the cumulative surface area of all the pores and voids present in a sample. Figure 11 shows the total pore surface area against dissolution time. The total pore surface area of nifedipine : Pluronic F-68 solid dispersion pellets increased linearly from 2 to 8 hr of dissolution time. This may be due to the formation of voids and pores as nifedipine and Pluronic F-68 were diffusing

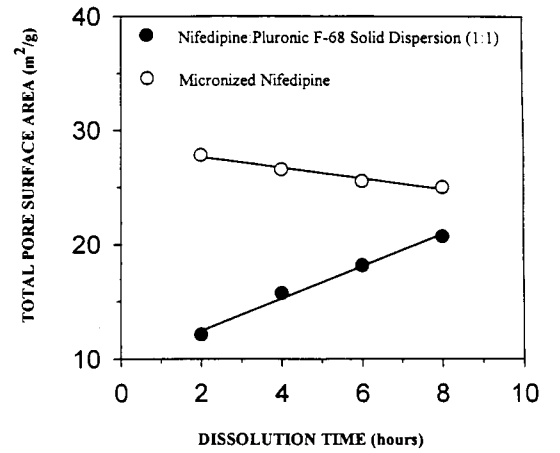

Figure 11. Effect of dissolution time on the changes in total pore surface area of the pellets.

out of the matrix. However, it is postulated that the total pore surface area is being reduced during dissolution, because the size of the pellets becomes smaller. Such a phenomenon can only occur if surface erosion is the only mechanism of release, as in fact was observed with nifedipine pellets. Their total surface area decreased linearly with dissolution time (Fig. 11). This confirms that surface erosion is the release mechanism of nifedipine pellets. In addition, the results demonstrated in Fig. 11 strongly indicate that upon incorporation of a poorly soluble drug

like nifedipine in erosion matrix pellet systems, a zero-order release for 12–24 hr is obtained, as described previously (7). However, a change in the physical properties and solubility of the drug as occurs with nifedipine : Pluronic F-68 solid dispersions alters the release profile and kinetics.

CONCLUSIONS

Controlled release of nifedipine following zero-order kinetics for 24 hr from a multi-unit erosion matrix was achieved. Drug release from nifedipine pellets occurred by matrix erosion. Drug release from pellets of nifedipine : Pluronic F-68 solid dispersion occurred by a combination of matrix erosion and diffusion mechanisms for 12 hr following first-order kinetics. The solubility of nifedipine was increased 10 times due to solid dispersion formation in 1 : 1 nifedipine : Pluronic F-68 ratio. Porosity parameters studied by mercury intrusion porosimetry proved that drug release was not influenced by the porosity of nifedipine pellets, however the drug release was controlled predominantly by porosity for nifedipine : Pluronic F-68 solid dispersion pellets.

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