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COMMUNICATION

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Eudragit Microcapsules of Nifedipine and Its Dispersions in HPMC–MCC: Physicochemical Characterization and Drug Release Studies

K. P. R. Chowdary and G. Girija Sankar

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam, 530 003, India

ABSTRACT

Nifedipine and its solid dispersions in hydroxypropyl methyl cellulose–microcrystalline cellulose (HPMC–MCC) were microencapsulated with Eudragit RL PM by an emulsion solvent evaporation method. The microcapsules are spherical, discrete, free flowing, and covered with a continuous coating of the polymer. XRD and DTA indicated the presence of nifedipine in solution form in the solid dispersions and their microcapsules. No chemical interaction between nifedipine and excipients in the microcapsules was observed. Nifedipine as such and its microcapsules gave very slow release because of its highly crystalline nature and poor solubility. Solid dispersion in HPMC–MCC gave fast and rapid dissolution of nifedipine. When these solid dispersions were microencapsulated a slow, controlled, and complete release over a period of 12 hr was observed from the resulting microcapsules. Drug release depended on the proportion of HPMC–MCC in the solid dispersion used as a core, coat:core ratio, and size of the microcapsules. Release was independent of pH and ionic strength. Drug release was governed by diffusion rate and followed first-order kinetics.

INTRODUCTION

Nifedipine (N) is used in the treatment of angina pectoris and hypertension. It is practically insoluble in water and its absorption is dissolution rate limited. Nifedipine has a short biological half-life of 3.4 hr (1) and is eliminated rapidly, and its antihypertensive effect lasts only a few hours. There are a few reports on the formulation of sustained-release products of nifedipine employing coated granules (2,3) and matrix tablets (4,5). In the present work microencapsulation by Eudragit was tried to obtain sustained release of nifedipine. As

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nifedipine is highly crystalline and poorly soluble, its solid dispersions in HPMC–MCC were prepared with a view to improving its dissolution rate and to evaluate the feasibility of using these dispersions as cores for microencapsulation to obtain sustained release. Nifedipine and its solid dispersions in HPMC–MCC were microencapsulated with Eudragit by an emulsion solvent evaporation (ESE) method and the resulting microcapsules were studied. The results are reported here.

EXPERIMENTAL

Materials

Nifedipine USP, Eudragit RL PM (Rohm GMBH Germany), hydroxypropyl methyl cellulose (having a viscosity of 50 cps in a 2% weight aqueous solution at 20°C), microcrystalline cellulose (MCC—Avicel, FMC Type, pH-105), acetone (Merck), methanol GR (Merck), dichloromethane (Merck), liquid paraffin IP, and petroleum ether (60°–80°C) were used.

Methods

All experiments were carried out under subdued light to prevent photodegradation of nifedipine.

Preparation of N–HPMC–MCC Solid Dispersions

Solid dispersions of nifedipine were prepared by dissolving nifedipine and HPMC in a solvent blend of methanol and dichloromethane (1:2) to obtain clear solution. MCC was then dispersed as fine particles and the solvent was removed by evaporation at 40°C under reduced pressure (8 in. Hg Abs). The mass obtained was then crushed, pulverized, and sifted through mesh No. 100.

Preparation of Microcapsules

Eudragit (0.2 g) was dissolved in acetone (5 ml) to form a homogeneous polymer solution. Core material, nifedipine or its solid dispersion (1.8 g), was added to the polymer solution and mixed thoroughly. The resulting mixture was then added in a thin stream to liquid paraffin (120 ml) contained in a 250-ml beaker while stirring at 100 rpm. A Remi Medium Duty Stirrer with Speed Meter (Model RQT 124) was used for stirring. Stirring was continued for 5 min to disperse the added mixture as fine droplets. The dispersion was transferred to a Buchner flask and stirring was continued with a magnetic stirrer. The solvent was then removed by evaporation at RT (28°C) under reduced pressure (8 in. Hg Abs) to produce spherical microcapsules. The microcapsules were collected by decantation and washed with petroleum ether to remove adhering liquid paraffin. The product was then air dried to obtain discrete microcapsules. In each case different proportions of coat to core materials, namely 1:9, 1:4, and 3:7 were used to prepare microcapsules with varying coat thickness. Nifedipine content of the dispersions and microcapsules was estimated by a known ultraviolet (UV) spectrophotometric method (2).

Size Analysis

For size distribution analysis, different sizes in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed.

SEM Study

The microcapsules were observed under a scanning electron microscope (SEM—JEOL, T330A, Japan). For SEM the microcapsules were mounted directly onto the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

X-ray Diffraction Study

X-ray powder diffraction patterns of nifedipine, its solid dispersions, and microcapsules were obtained using Philips X-ray Powder Diffractometer (Model PW 1729) employing Fe-K_α radiation. The diffractograms were run at 2.4°/min in terms of 2θ angle.

Differential Thermal Analysis

Differential thermal analysis (DTA) was performed on nifedipine, its solid dispersions, and microcapsules using a Stantan Redcroft DTA 673-4 Analyser with RE 571-20 Potentiometric Recorder. The samples were subjected to heating in the range 50°–300°C at a rate of 10°C/min.

IR Spectra

IR spectra of nifedipine and its microcapsules were obtained using a Shimadzu IR-408 Spectrophotometer.

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IR spectra were obtained by preparing solid disks in KBr, using KBr as reference.

Dissolution Rate Studies on Solid Dispersions

The dissolution rate of nifedipine in pure form, from various solid dispersions was studied using the USP XXI Dissolution Rate Test Apparatus employing a paddle stirrer. In 900 ml of dissolution medium (0.1 N HCl containing 10% methanol), a sample equivalent to 10 mg of nifedipine, a speed of 50 rpm, and a temperature of 37° ± 1°C were employed in each test. A 5-ml aliquot of dissolution medium was withdrawn at different time intervals, suitably diluted, and assayed spectrophotometrically at 238 nm using a Shimadzu UV-150 double-beam spectrophotometer.

Drug Release Studies on Microcapsules

Release of nifedipine from the microcapsules of size 20/35 and 35/50 was studied using an oscillating tube dissolution rate apparatus as per NF XIII procedure. Dissolution fluid consisted of 900 ml of simulated gastrointestinal fluids of increasing pHs namely pH 1.2 (0–1 hr), pH 2.5 (1–2 hr), pH 4.5 (2–3.5 hr), pH 7.0 (3.5–5 hr) and pH 7.5 (5–12 hr). The dissolution fluid also contained 10% methanol to maintain sink condition. A sample of microcapsules equivalent to 20 mg of nifedipine and a speed of 36 cycles per minute were employed in each test. Samples withdrawn were assayed at 238 nm for nifedipine.

RESULTS AND DISCUSSION

The microcapsules prepared (Table 1) were found to be discrete, spherical, and free flowing. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained. The size analysis of different microcapsules showed that generally about 18% and 70% were in the size range of −20 +30 (670 μm) and −35 +50 (398.5 μm) mesh size, respectively. A log-normal size distribution of the microcapsules was observed in all the batches prepared. Low CV (<1.5) in percent drug content indicated uniformity of drug content in each batch of microcapsules. Drug content of the microcapsules was found to be the same in different sieve fractions. Scanning electron microscopy (SEM—Fig. 1) indicated that the microcapsules are discrete, spherical, and covered with continuous coating of Eudragit.

X-ray diffractograms of nifedipine exhibited characteristic diffraction pattern, whereas in the case of N-HPMC-MCC (2:2:6) solid dispersion and its microcapsules the sharp diffraction peaks of nifedpine have disappeared (Fig. 2). The lack of sharp peaks in

Table 1

Eudragit Microcapsules Prepared and Their Nifedipine Contents

Mico-capsules	Core	Core:Coat Ratio Employed	Percent Drug Content, Mean (CV) For Size 20/35	For Size 35/50
MC1	N	9:1	88.28 (0.405)	89.64 (0.672)
MC2	H-HPMC-MCC (2:2:6)	9:1	17.76 (1.496)	17.00 (0.449)
MC3	H-HPMC-MCC (2:2:6)	8:2	14.90 (1.01)	15.10 (0.530)
MC4	H-HPMC-MCC (1:2:7)	9:1	8.96 (1.267)	8.89 (0.437)
MC5	H-HPMC-MCC (1:2:7)	8:2	8.01 (1.09)	7.94 (0.652)
MC6	H-HPMC-MCC (1:2:7)	7:3	6.82 (0.371)	7.05 (0.918)

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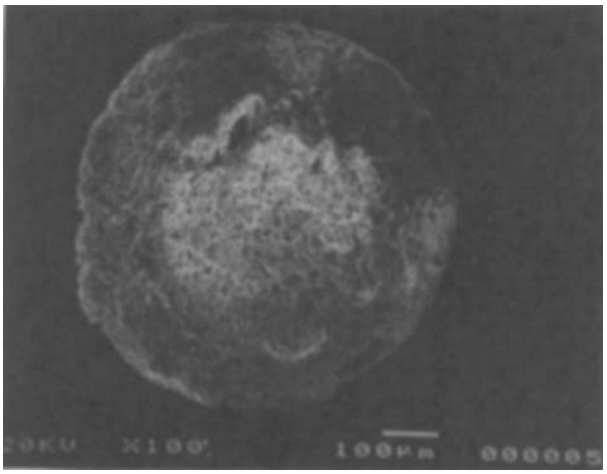

Figure 1. SEM photograph of microcapsules MC2.

the diffractograms of solid dispersions and their microcapsules indicates that the drug is either in an amorphous phase or in solution form in the polymer HPMC.

The DTA thermograms of nifedipine, N-HPMC-MCC (2:2:6) solid dispersion, and its microcapsules MC2 are shown in Fig. 3. Nifedipine exhibited an endothermic peak at 171°C. The thermograms of solid dispersion and its microcapsules showed no peaks, indicating that nifedipine is present in solution state in the polymer HPMC of the solid dispersion. The DTA results thus confirmed the existence of nifedipine in solution form in the solid dispersion and its microcapsules.

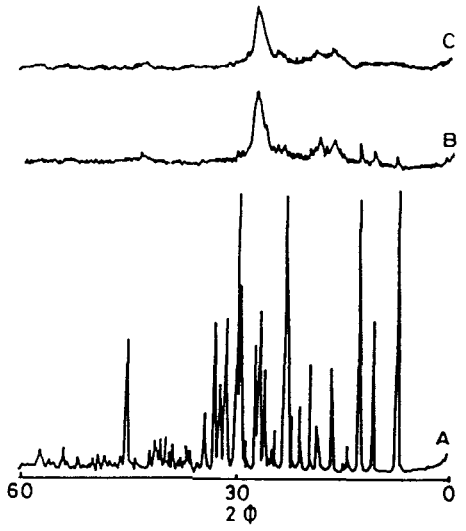

Figure 2. X-ray diffractograms of A, Nifedipine; B, N-HPMC-MCC (2:2:6) solid dispersion; C, microcapsules MC2.

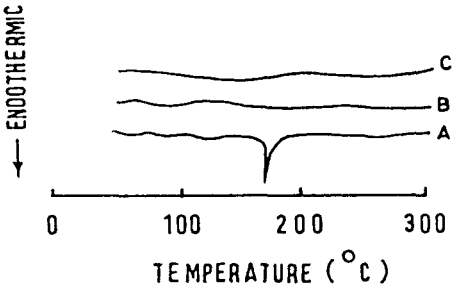

Figure 3. DTA thermograms of A, nifedipine; B, N-HPMC-MCC (2:2:6) solid dispersion; C, microcapsules MC2.

The IR spectra of nifedipine, N-HPMC-MCC (2:2:6) solid dispersion, and its microcapsules were all identical. The principal IR absorption peaks of nifedipine at 1121 cm^{-1} (-C-O- ester), 1380 cm^{-1} ($-C-CH_3$), 1530 cm^{-1} (NO_2), 1625 cm^{-1} (-C=C- aromatic), and 1689 cm^{-1} (C=O ester) were all observed in the spectra of nifedipine as well as its solid dispersion and microcapsules. These spectral observations indicated no chemical interaction between nifedipine and other excipients used.

Nifedipine release from various microcapsules was studied in simulated gastrointestinal fluids for a period of 12 hr. When nifedipine was microencapsulated with Eudragit, the release from the microcapsules was found to be very low, 33% in 12 hr. Unencapsulated nifedipine also showed very slow dissolution (Fig. 4).

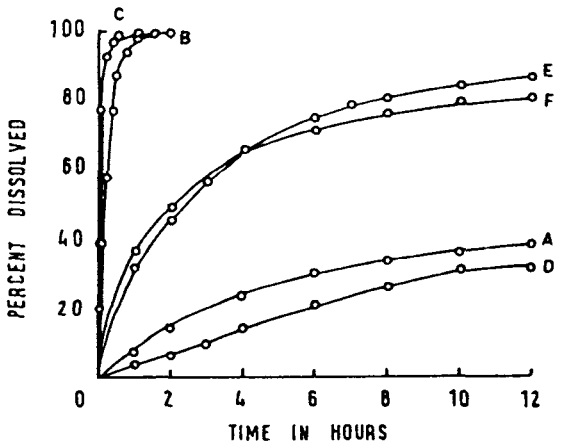

Figure 4. Dissolution profiles of nifedipine (A); solid dispersions N-HPMC-MCC 2:2:6 (B) and 1:2:7 (C); and microcapsules (size 35/50) MC1 (D), MC2 (E), and MC6 (F).

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Table 2

Nifedipine Release from Eudragit Microcapsules in Simulated Gastrointestinal Fluids

Micro-capsules	Percent Nifedipine Released at 4 Times (hr)				Release Rate Constant k_1 (hr^{-1})
	2	4	8	12	
Size 20/35					
MC1	4.93	12.01	22.14	24.75	0.0247
MC2	30.21	43.65	56.94	63.33	0.1157
MC3	29.08	37.45	43.90	46.78	0.0986
MC4	84.50	98.98	98.99	98.99	0.5880
MC5	70.84	86.90	96.69	98.80	0.4960
MC6	49.73	59.81	68.82	74.44	0.2020
Size 35/50					
MC1	6.09	14.09	27.24	32.61	0.0343
MC2	45.35	65.90	80.47	86.61	0.2181
MC3	36.80	52.37	64.20	69.46	0.1467
MC4	95.64	99.46	99.50	99.50	0.9290
MC5	81.64	92.62	97.91	97.98	0.5944
MC6	51.05	65.04	76.12	80.02	0.2070

The poor dissolution and low release of nifedipine from the microcapsules is due to the highly crystalline nature and poor solubility of nifedipine. The various attempts made to improve the dissolution of nifedipine include solid dispersion in water-soluble carriers such as urea (6), polyvinyl pyrrolidone (PVP) (7), propylene glycol (6), PVP–MCC, and HPC–MCC (8); and complexation with cyclodextrins (9).

In the present work solid dispersions of nifedipine in HPMC–MCC were prepared with a view to improving its dissolution rate. MCC was included in the dispersions as a diluent to increase the bulk as nifedipine is a low-dose drug. The solid dispersions gave rapid dissolution of nifedipine when compared to nifedipine pure drug: 90% dissolution was observed in 45 min in the case of N–HPMC–MCC (2:2:6) dispersion, and in 10 min in the case of N–HPMC–MCC (1:2:7) dispersion.

When nifedipine solid dispersions in HPMC–MCC were microencapsulated, a slow, controlled, and complete release spread over a period of 12 hr (Table 2) was observed. Nifedipine release from these microcapsules followed first-order kinetics.

Nifedipine release from these microcapsules depended on composition of the core, coat:core ratio, and size of the microcapsules. As the proportion of coat increased, nifedipine release decreased. The release increased as the size of the microcapsules decreased.

The drug release mechanism from the microcapsules was diffusion controlled as plots of the amount of the drug released versus square root of time were found to

Table 3

Nifedipine Release from Microcapsules MC2 (Size 35/50) in Acidic and Alkaline Fluids of Varying Ionic Strengths

Dissolution Fluid	Percent Nifedipine Released at 4 Times (hr)			
	1	2	3	4
0.1 M HCl (pH 1.2)	33.46	45.30	54.56	65.92
Phosphate buffer (pH 7.5, 0.01 M)	34.21	44.26	53.65	64.29
Phosphate buffer (pH 7.5, 0.05 M)	33.78	45.74	54.72	65.69

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be linear. Nifedipine release was found to be similar and to the same extent in both acidic and alkaline fluids as well as at different ionic strengths of the dissolution fluids (Table 3).

Thus slow, controlled, and complete nifedipine release, independent of pH and ionic strength, over a period of 12 hr was obtained by microencapsulation of its solid dispersions in HPMC–MCC, which was not possible with either nifedipine alone or its solid dispersions. Nifedipine release from these microcapsules could be controlled by varying the proportion of HPMC–MCC in the solid dispersion used as core, core:coat ratio in the preparation of microcapsules, and size of the microcapsules.

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