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COMMUNICATIONS

CONTROLLED NIFEDIPINE RELEASE FROM MICROCAPSULES OF ITS DISPERSIONS IN PVP-MCC AND HPC-MCC

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ABSTRACT

Nifedipine and its solid dispersions in polyvinyl-pyrrolidone-microcrystalline cellulose (PVP-MCC) and hydroxypropyl cellulose - microcrystalline cellulose (HPC-MCC) were microencapsulated with cellulose acetate by an emulsion solvent evaporation method. The microcapsules are spherical, discrete and free flowing. Nifedipine as such and its microcapsules gave very slow release because of its highly crystalline nature and poor solubility. Solid dispersion in PVP-MCC and HPC-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 hours was observed from the resulting microcapsules. Drug release depended on the proportion of PVP-MCC and HPC-MCC in the solid dispersions used as core, coat : core ratio and size of the microcapsules and the release was pH independent. 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 3.43 hrs (1) and is eliminated rapidly and its antihypertensive effect lasts only for 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 was tried to obtain controlled release of nifedipine. As nifedipine is highly crystalline and poorly soluble, its

solid dispersions in PVP-MCC and HPC-MCC were prepared with a view to improve its dissolution rate and to evaluate the feasibility of using these dispersions as core for microencapsulation to obtain controlled release. MCC was included in the dispersions as a diluent to increase the bulk as nifedipine is a low dose drug. Nifedipine and its solid dispersions in PVP-MCC and HPC-MCC were microencapsulated with cellulose acetate by an emulsion solvent evaporation method and the resulting microcapsules were studied. Cellulose acetate, a non toxic cellulose polymer having good film forming properties is suitable for microencapsulation for controlled release (6,7). The results are reported here.

EXPERIMENTAL

Materials

Nifedipine B.P., cellulose acetate (D.P. 250-360; having a viscosity of 3 cps in a 2% concentration by weight solution in acetone at 25°C), polyvinyl-pyrrolidone (BASF; PVP K-30; Mol. wt. 40,000), hydroxypropyl cellulose - SL (HPC) (Nisso; having a viscosity of 3.0-5.9 cps in a 2% by weight aqueous solution at 20°C), microcrystalline cellulose (MCC) (Avicel, FMC Type pH-105), acetone (Merck), methanol (Merck), Liquid paraffin I.P. and petroleum ether (60-80°C) were used.

Methods

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

Preparation of Solid Dispersions

Solid dispersions of nifedipine were prepared by dissolving nifedipine and PVP or HPC in methanol to get a clear solution. MCC was then dispersed as fine particles and the solvent is removed by evaporation at 40°C under vacuum (0.86 torr). The mass obtained was then crushed, pulverised and sifted through mesh No.100.

Preparation of Microcapsules

Cellulose acetate (0.2 g) was dissolved in acetone (8ml) 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 minutes 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 R.T. (28°C) under vacuum (0.86 torr) 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 two different proportions of coat to core materials namely 1:9 and 1:4 were used to prepare microcapsules with varying coat thickness. Nifedipine content of the dispersions and microcapsules was estimated by a known 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 and 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 and its solid dispersions were obtained using an X-ray powder diffractometer (Miniflex Tabletop X-ray diffractometer JP Rigaku) employing Cu-K_α radiation. The diffractograms were run at 2°/min in terms of 2θ angle.

Differential Scanning Calorimetry

Du Pont Model 2100 Differential Scanning Calorimeter was used. The samples were sealed in aluminium pans and the DSC thermograms were recorded at a heating rate of 10°C/min from 50 to 300°C in an atmosphere of nitrogen.

Dissolution Rate Studies on Solid Dispersions

The dissolution rate of nifedipine in pure form, from various solid dispersions was studied using USP XXI Dissolution Rate Test Apparatus employing a paddle stirrer. In 900 ml of dissolution medium (0.1N HCl), a sample equivalent to 12 mg of nifedipine, a speed of 50 rpm and a temperature of 37°C±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 Shimadzu UV-150 spectrophotometer. Dissolution efficiency (D.E.) values were calculated from the dissolution profiles as suggested by Khan (8). The dissolution parameters calculated are given in Table 2.

Drug Release Studies on Microcapsules

Release of nifedipine from the microcapsules of size 20/35 and 35/50 was studied using Oscillating tube dissolution rate apparatus as per NF XIII procedure. Dissolution fluid consisted of 900ml of simulated gastrointestinal fluids of increasing pH namely pH 1.2 (0-1 hr), pH 2.5 (1-2 hrs), pH 4.5 (2-3.5 hrs), pH 7.0 (3.5-5.00 hrs) and pH 7.5 (5-12 hrs). The dissolution fluids also contained 20% 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 20% and 65% were in the size range of -20+35 (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 c.v. in per cent drug content indicated uniformity of drug content in each batch of microcapsules. Drug content of the microcapsules was also found to be the same in different sieve fractions. SEM photograph (Fig.1) indicated that the microcapsules are discrete, spherical and covered with continuous coating of cellulose acetate.

Nifedipine release from various microcapsules was studied in simulated gastrointestinal fluids for a period of 12 hours. When nifedipine alone was micro-encapsulated with cellulose acetate, the release from the microcapsules was found to be very low (Table 3). This low release is due to the highly crystalline nature and poor solubility of nifedipine.

Solid dispersions of nifedipine in PVP, HPC, PVP-MCC and HPC-MCC were prepared with a view to improve its dissolution rate and efficiency. The solid dispersions gave rapid dissolution of nifedipine when compared to nifedipine pure drug. The dissolution of nifedipine in pure form and from various solid dispersions obeyed Hixson-Crowell's cube root dissolution rate equation (9) and the corresponding rate constants are given in Table 2. Among the solid dispersions prepared N-PVP-MCC (2:2:6) and N-HPC-MCC (2:2:10) gave highest dissolution rates. A 17 and 23 fold increase in dissolution rate was observed with these dispersions respectively. The dissolution efficiency of nifedipine was increased from

TABLE 1

Nifedipine Microcapsules Prepared and their Drug Contents

Micro-capsules	Core	Core: Coat ratio employed	Per cent drug content Mean (c.v.) For size 20/35	For size 35/50
MC1	N	9:1	91.78 (0.479)	91.35 (1.740)
MC2	N-PVC-MCC (4:2:4)	9:1	35.83 (1.220)	35.72 (1.604)
MC3	N-PVP-MCC (4:2:4)	8:2	32.27 (1.812)	31.86 (1.340)
MC4	N-PVP-MCC (2:2:6)	9:1	18.35 (0.204)	18.21 (0.132)
MC5	N-PVP-MCC (2:2:6)	8:2	16.44 (0.407)	16.83 (2.846)
MC6	N-HPC-MCC (2:2:6)	9:1	19.06 (1.57)	19.08 (1.14)
MC7	N-HPC-MCC (2:2:6)	8:2	15.47 (1.29)	15.85 (0.63)
MC8	N-HPC-MCC (2:2:10)	9:1	13.14 (1.14)	13.20 (2.70)
MC9	N-HPC-MCC (2:2:10)	8:2	11.12 (0.41)	10.45 (0.93)

8.75% for pure drug to 66.6% in the case of N-PVP-MCC (2:2:6) and 61.6% in the case of N-HPC-MCC (2:2:10) solid dispersions. X-ray diffractograms of nifedipine exhibited characteristic diffraction pattern, whereas in the case of solid dispersions sharp diffraction peaks of nifedipine have disappeared (Fig.2). The lack of sharp peaks in the diffractograms indicates that the drug is either in an amorphous phase or in solution form in the polymer PVP or HPC. The DSC thermograms of nifedipine, PVP, HPC, N-PVP-MCC (2:2:6) and N-HPC-MCC (2:2:10) solid dispersions are shown in Fig. 3. Nifedipine exhibited an endothermic peak at 174.31°C. PVP exhibited a broad endothermic peak at 122.74°C whereas no peak was observed with HPC. The thermograms of the two solid dispersions, N-PVP-MCC and N-HPC-MCC showed no nifedipine peaks, indicating that nifedipine is present

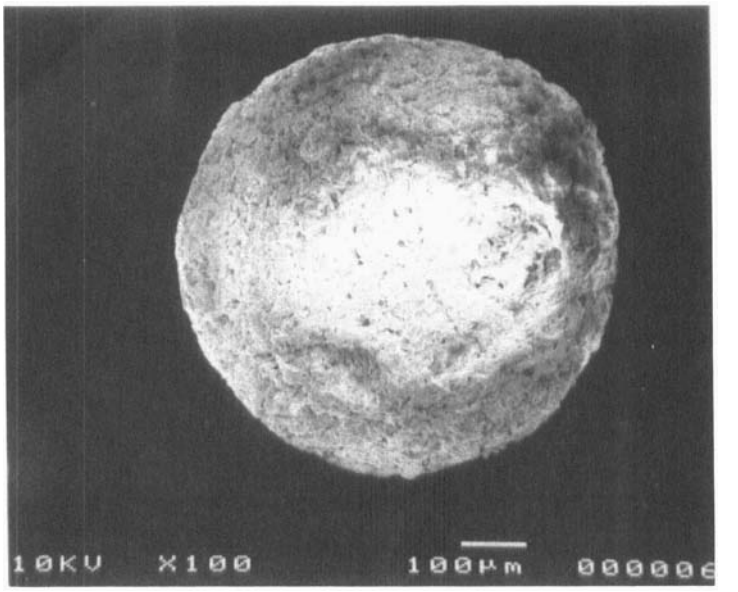

FIGURE 1

SEM Photograph of Microcapsules MC4

TABLE 2

Drug content and dissolution parameters of various solid dispersions

Solid dispersion	Per cent drug content	Dissolution efficiency (%) mean (cv)	Cube root dissolution rate constant ($mg^{1/3}$ min^{-1}) mean (cv)
Nifedipine	--	8.75(2.28)	0.002(2.38)
N-PVP (9:1)	88.6 ± 0.01	22.50(1.55)	0.006(4.35)
N-PVP (4:1)	81.46 ± 0.98	33.30(1.20)	0.013(3.47)
N-HPC (9:1)	88.60 ± 0.04	20.40(1.56)	0.005(2.00)
N-HPC (4:1)	78.13 ± 0.05	28.33(3.38)	0.010(1.05)
N-PVP-MCC (4:2:4)	42.10 ± 1.04	51.45(1.94)	0.026(3.84)
N-PVP-MCC (2:2:6)	18.16 ± 1.09	66.60(1.57)	0.035(2.85)
N-HPC-MCC (2:2:6)	21.20 ± 0.03	56.60(1.91)	0.031(1.61)
N-HPC-MCC(2:2:10)	14.36 ± 0.02	61.66(1.37)	0.047(2.12)

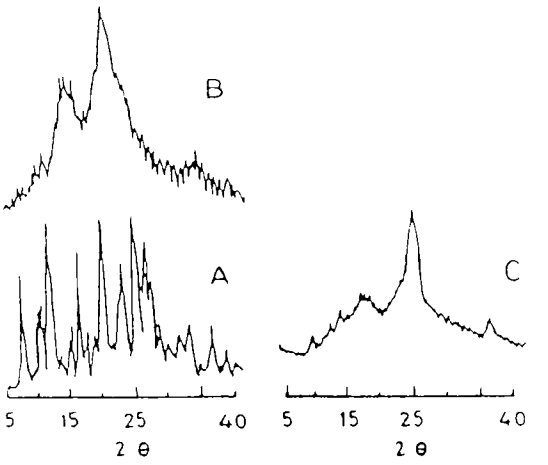

FIGURE 2

X-ray diffractograms of A : Nifedipine, B : N-HPC-MCC (2:2:10); C : N-PVP-MCC (2:2:6) solid dispersions.

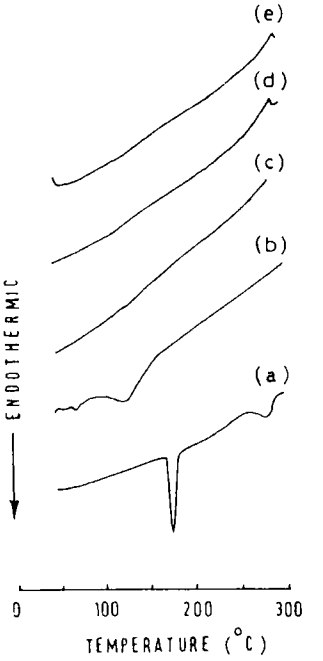

FIGURE 3

DSC thermograms of A : Nifedipine; B : PVP; C : HPC; D:N-PVP-MCC (2:2:6) and E : N.HPC-MCC (2:2:10) solid dispersions

TABLE 3

Nifedipine Release from various Microcapsules in simulated g.i. fluids

Micro capsules	Percent Nifedipine released in hours				Release Rate Constant K_1 (hr^{-1})
	2	4	8	12	
Size 20/35					
MC1	8.61	12.62	18.92	23.03	0.019
MC2	22.33	36.56	48.10	54.27	0.060
MC3	15.38	20.82	31.64	35.82	0.035
MC4	39.64	54.32	80.84	93.70	0.218
MC5	32.84	48.14	66.25	72.50	0.102
MC6	29.37	43.72	63.50	71.26	0.101
MC7	28.31	40.84	52.92	59.69	0.070
MC8	34.32	53.57	75.15	84.38	0.156
MC9	27.82	40.36	57.28	66.45	0.087
Size 35/50					
MC1	9.15	14.25	20.97	24.40	0.023
MC2	27.40	43.10	53.70	62.90	0.077
MC3	18.33	29.40	43.30	52.36	0.060
MC4	42.50	60.00	83.46	97.60	0.271
MC5	35.50	50.22	72.90	86.60	0.159
MC6	40.52	55.14	73.44	85.36	0.150
MC7	28.60	42.44	57.59	64.79	0.083
MC8	43.00	65.00	89.76	98.75	0.264
MC9	36.67	53.25	69.87	80.07	0.127

in solution state in the polymers of the solid dispersions. The DSC results thus confirmed the existence of nifedipine in solution form in the solid dispersions. As nifedipine is in solution form in the solid dispersions it produced faster dissolution.

When nifedipine solid dispersions in PVP-MCC and HPC-MCC were microencapsulated, a relatively fast but controlled and complete release spread over a period of 12 hours (Table 3) 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

TABLE 4

Nifedipine Release from Selected Microcapsules (size 35/50) in Acidic and Alkaline Fluids

Micro-capsules	Percent Nifedipine Released in 0.1N HCl(pH 1.2)			Phosphate Buffer(pH 7.4)		
	1hr	2hrs	4hrs	1hr	2hrs	4hrs
MC1	5.82	8.91	14.57	6.08	8.74	13.88
MC2	16.19	22.37	32.05	14.74	21.85	32.05
MC4	26.45	34.10	45.34	25.79	33.59	45.77
MC8	32.31	47.22	60.08	30.42	45.25	58.02

the size of the microcapsules decreased. 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 be linear. Nifedipine release was found to be similar and to the same extent in both acidic (0.1N HCl) and alkaline (phosphate buffer pH 7.4) fluids (Table 4).

Thus controlled nifedipine release, independent of pH was obtained by microencapsulation of its solid dispersions in PVP-MCC or HPC-MCC. Nifedipine release from these microcapsules could be controlled by varying the proportion of PVP-MCC or HPC-MCC in the solid dispersions used as core, core:coat ratio in the preparation of microcapsules and size of the microcapsules.

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