
Microencapsulation of Nifedipine - MCC Solvent deposited System for Sustained Release

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Nifedipine and its solvent deposited systems on Microcrystalline Cellulose (MCC) were microencapsulated with cellulose acetate by an emulsification solvent evaporation method and the microcapsules were studied. Microcapsules containing Solvent Deposited (SD) systems as core gave slow, sustained and complete release of nifedipine over a period of 12 hours which was not possible with microcapsules of nifedipine alone. The release depended on proportion of MCC in the SD systems used as core, coat; core ratio and size of the microcapsules. Release was diffusion controlled.

ALTHOUGH sustained release drug delivery systems have been used in other areas of medicine, their application in the treatment of angina and hypertension is relatively recent. Nifedipine is practically insoluble in water and its absorption is dissolution rate limited. It has a short biological half-life¹ of 2-3 and is eliminated rapidly from the body. Its effects last only for a few hours and it needs to be administered three to four times a day. Hence to improve its therapeutic efficacy and patient compliance sustained release dosage forms are needed for nifedipine. There are few reports on the formulation of sustained release products of nifedipine employing coated beds,^{2,3} matrix tablets^{4,5} and complexation.⁶ in the present work microencapsulation with cellulose acetate was tried to obtain sustained release of nifedipine. As nifedipine is practically insoluble in aqueous fluids, both acidic and alkaline, it was first solvent deposited on MCC to improve its dissolution rate. The nifedipine - MCC SD systems were then microencapsulated to obtain sustained release. The feasibility of using SD systems as core in microencapsulation was investigated. The results are reported here.

EXPERIMENTAL

MATERIALS

Nifedipine B.P. (Noble Medicure Pvt. Ltd., Belgaum), microcrystalline cellulose (SD Fine Chem), cellulose acetate (DP 250 - 360; having a viscosity of 3 cps in a 2% concentration by weight solution in acetone at 25°C), methanol AR (Ranbaxy Chemicals), Acetone AR (Ranbaxy Chemicals), cyclohexane AR (SD Fine Chem), Petroleum ether (60° - 80°) AR (SD Fine Chem), Liquid paraffin, I.P. were used.

METHODS

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

Preparation of SD systems of nifedipine

Nifedipine was dissolved in methanol. To the clear solution MCC was added and mixed to disperse. The solvent was then evaporated at room temperature under reduced pressure (8 in Hg.abs). The mass obtained was collected and dried at 40°.

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The dried mass was powdered and passed through mesh no. 100.

Three different proportions of drug : excipient; 1:4, 1:9, and 1:19 were used to prepared nifedipine - MCC SD systems.

Microcapsule Preparation

Cellulose acetate microcapsules containing nifedipine or its SD systems as core were prepared by emulsification solvent evaporation (ESE) method.⁷

Cellulose acetate (0.2 g) was dissolved in acetone (8 ml) to form a homogeneous polymer solution. Core material (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 (Ptek stirrer). 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 R.T. (28°) 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 two different proportions of coat to core (1:9 and 2:8) were used to prepare microcapsules with varying coat thickness. The microcapsules prepared and their composition are given in Table-1.

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.

Drug Content

From each batch of microcapsules for samples of 10 mg each were taken and analysed for nifedipine content at 238 nm. The method obeyed Beer's law in the concentration range of 0 to 10 µg/ml.

SEM Study:

The microcapsules were observed under Scanning Electron Microscope (SEM, HITACHI, JAPAN). For SEM the microcapsules were mounted directly on the SEM sample stub using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

Drug release study

Release of nifedipine from various microcapsules was studied in simulated gastric fluid (SGF) of pH 1.2 up to 2 hours and in simulated intestinal fluid (SIF) of pH 7.4 from 2 to 12 hours using USP XXI Dissolution Rate Test Apparatus employing basket stirrer. The dissolution fluids contained 20% methanol to maintain sink condition.

900 ml of the SGF was taken in the dissolution vessel. A sample of microcapsules equivalent to 20 mg of nifedipine in a hard gelatin capsule was taken into the basket. A speed of 50 rpm and temperature $37^{\circ} \pm 1^{\circ}$ were maintained throughout the experiment. At the end of 2 h the dissolution fluid was replaced with SIF of pH 7.4 and the experiment was continued for 12 h. Dissolution fluid samples withdrawn at different time intervals were assayed at 238 nm for nifedipine. At the end of the experiment the remaining microcapsules are collected and the amount of nifedipine remaining in the microcapsules was estimated and used in calculating the percent nifedipine released at various times. The percent of nifedipine released at various times was calculated and plotted against time (Fig.2 and 3).

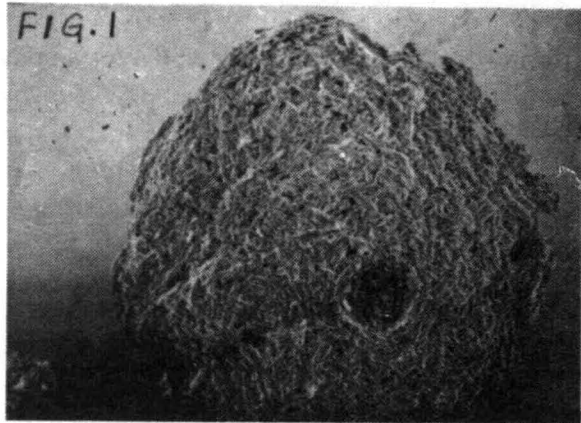


Fig. 1 : SEM Photographs of Microcapsules CA 5

RESULTS AND DISCUSSION

The ESE method used for the preparation of CA microcapsules resulted in relatively large sized microcapsules with both nifedipine and its SD systems. The microcapsules could readily be separated into various sizes by sieving and more uniform size range of microcapsules could readily be obtained. The size analysis of different microcapsules showed that generally about 65 to 70% were in the size range of -20+50 mesh size. A log-normal size distribution of microcapsules was observed in all the batches prepared.

Coefficient of variation (c.v) in the percent drug content (Table-1) was found to be less than 3% in all the batches indicating uniformity of drug content. Drug content of the microcapsules was also found to be the same in different sieve fractions.

The SEM photographs (Fig.1) of microcapsules indicated that the microcapsules were discrete, spherical and covered with continuous coating of the coat material.

Nifedipine release was found to be very low (16-23% in 12 h.) with microcapsules containing nifedipine as core (Fig. 2 and 3). Nifedipine release from the microcapsules was found to be nearly the same and to the same extent in both acidic (pH 1.2) and alkaline

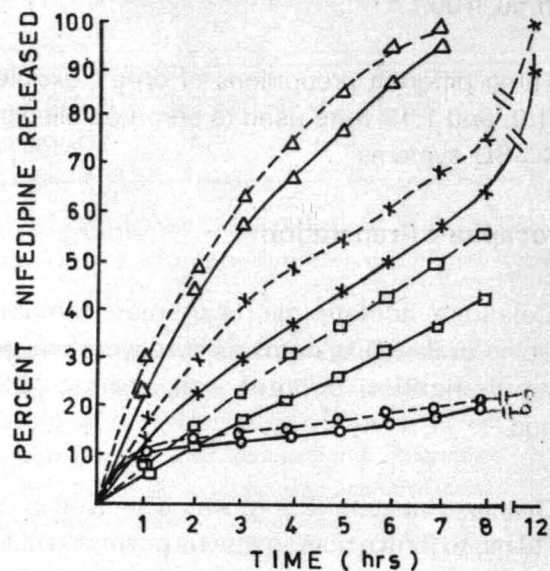


Fig. 2 : Drug Release Profiles of Microcapsules CA1 (O) CA3 (□) CA5 (X) and CA7 (Δ); size 20/35 (—) Size 35/50 (- - -).

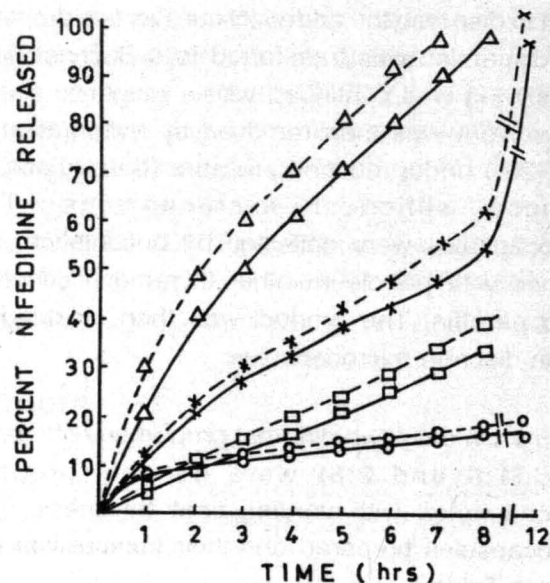


Fig. 3 : Drug Release Profiles of Microcapsules CA2 (O) CA4 (□), CA6 (X) and CA8 (Δ); Size 20/35 (—) size 35/50 (- - -).

(pH 7.4) fluids. The very slow release observed with microcapsules with microcapsules containing

Table 1 : Cellulose Acetate Microcapsules Prepared, their Composition and Drug Release Rate Constant

Micro-capsules	Core	Coat : Core ratio	Percent drug content		$(K_1(\text{hr}^{-1}))$	
			Mean (c.v.)			
			20/35 Size	35/50 Size	20/35 Size	35/50 Size
CA1	N	1:9	90.22 (0.681)	90.43 (0.940)	0.018	0.032
CA2	N	2:8	80.37 (0.401)	80.17 (0.603)	0.015	0.017
CA3	N-MCC (1:4)	1:9	17.17 (0.557)	17.02 (0.562)	0.065	0.095
CA4	N-MCC (1:4)	2:8	15.12 (0.63)	15.45 (1.239)	0.040	0.061
CA5	N-MCC (1:9)	1:9	8.62 (1.110)	8.72 (1.403)	0.109	0.148
CA6	N-MCC (1:9)	2:8	7.92 (1.20)	7.7 (1.876)	0.092	0.115
CA7	N-MCC (1:19)	1:9	3.8 (2.14)	3.77 (2.53)	0.09	0.307
CA8	N-MCC (1:19)	2:8	3.62 (2.65)	3.62 (2.65)	0.242	0.348

N = Nifedipine; K_1 = First order release rate constant

nifedipine as core is due to the highly crystalline nature and poor aqueous solubility of nifedipine. As such microcapsules containing nifedipine as core are not suitable for sustained release. When nifedipine - MCC solvent deposited systems were microencapsulated, a slow, controlled and complete release spread over a period of 12 h was observed. Nifedipine release from microcapsules containing SD systems as core was found to be higher than that observed with microcapsules containing nifedipine as core. Nifedipine release from these microcapsules followed first order kinetics. The first order release rates are given in Table -1. The release rate increased as the proportion of MCC in the SD system

employed as core was increased. The release rate decreased as the proportion of coat (CA) increased. Percent of nifedipine released from the microcapsules increased as the size of microcapsules decreased. The nifedipine release from these microcapsules depended on the coat: core ratio, size of the microcapsules and proportion of MCC in the SD systems employed as core. Plots of amount of drug released versus $\sqrt{\text{time}}$ (Fig.4) were found to be linear with all the microcapsules indicating that the drug release mechanism from these microcapsules might be of diffusion type as proposed by Higuchi.⁸ The improved, complete and sustained release of nifedipine observed with microcapsules

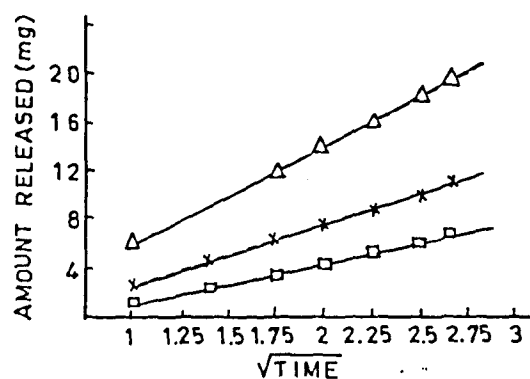


Fig. 4 : Amount released versus $\sqrt{\text{time}}$ plots of Microcapsules CA4, (□), CA6 (X), and CA8 (Δ) of size 20/35.

containing SD system as core is may be due to the molecular micronization that the drug undergoes while depositing on the surface of MCC.

CONCLUSION

SD systems of nifedipine could be used as core and can be microencapsulated by ESE method. The resulting large sized spherical microcapsules gave slow, sustained and complete release of nifedipine over a period of 12 hours which was not possible with microencapsulation of nifedipine alone. The desired

release can be achieved by altering the proportion of MCC in the SD system used as core, coat; core ratio and size of the microcapsules.

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