DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(13), 2057-2075 (1990)

POLYACRYLATE (Eudragit Retard) MICROSPHERES FOR ORAL CONTROLLED RELEASE OF NIFEDIPINE. I. FORMULATION DESIGN AND PROCESS OPTIMIZATION.

A. Barkai, Y.V. Pathak and S. Benita*

Department of Pharmacy, School of Pharmacy, The Hebrew University of Jerusalem, P.O. Box 12065, Jerusalem 91120, Israel.

ABSTRACT

Nifedipine was incorporated in polyacrylate-polymethacrylate microspheres using the solvent evaporation process. Optimal experimental conditions were found for the production of large batches of nifedipine microspheres based on Eudragit polymers the amount of which ranged from 25 to 40g. It was noted that the microspheres were not quite spherical and some of them especially the large microspheres, collapsed and lost their spherical shape due to the existence of internal void volume as evidenced by SEM examination of fractured nifedipine microspheres. It appeared that the experimental conditions used in the present study favoured the formation of microspheres of a new type. They could be defined as "film type" microspheres which consisted of spherical micromatrices comprizing an internal void space and a polymeric membrane of variable thickness where the nifedipine was dispersed either in a molecular or solid state depending on the payload extent. This was confirmed by differential scanning calorimetry analysis and scanning electron microscopy which detected drug crystals embedded on the microsphere surfaces at high drug content.

*Author for correspondence: Dr. Simon Benita

INTRODUCTION

Polyacrylate-polymethacrylate copolymers (Eudragits) are widely used as tablet adjuvants and coating polymers.[1] These polyacrylate polymers were also used for the microencapsulation of paracetamol, indomethacin and theophylline by means of a coacervation method involving phase separation from chloroform by a non-solvent addition technique.[2,3] Because of their various interesting properties, which can offer advantageous possibilities as oral controlled release formulations, these Eudragit polymers have recently received increased attention as microsphere wall materials.[4-8]

Nifedipine, a systemic calcium channel blocking agent, practically insoluble in water and light-sensitive was selected since the drug exhibits all the required pharmacokinetic and physicochemical properties which make it a good candidate to be incorporated in a controlled release dosage form. Therefore, nifedipine has been incorporated in microspheres of Eudragit RS and RL. The polyacrylate microspheres were prepared using the solvent-evaporation technique previously reported[4]. Production variables have been tested for the purpose of defining conditions for the design and production of large batches of these microspheres.

MATERIALS AND METHODS

Nifedipine conformed to USP XXI, Eudragit RS and RL were kindly provided by Roehm Pharma GmbH (Darmstadt, Germany), polyvinyl alcohol (PVA), MW of 14000 was supplied by BDH Laboratory (Poole, UK).

Preparation of nifedipine microspheres on a small scale (2.5 gm per batch of microspheres)

The exact preparation method previously reported was used[4]. Various amounts of nifedipine (50-1200mg) were incorporated into a 2g mixture of Eudragit RS and RL (1:1).

Method of preparation of large batches of nifedipine microspheres.

After preparing a large number of batches in preliminary studies, the following optimal experimental conditions were finalized for the production of nifedipine microspheres. One liter of water containing 0.8% PVA was placed in a three litre glass beaker. A solution comprizing 25 gm of Eudragit RS:RL mixture (1:1) and nifedipine (1.25 to 12.5 gm) in a known amount of methylene chloride (60-100 ml), was added to the aqueous phase through a separate funnel (4 cm diameter). The mixture was stirred at a constant rate by an Heidolph Stirrer fitted with a digital counter and a four blade impeller having a diameter of 15 cm.. The agitation rate was varied from 200 to 750 rpm. The resulting emulsion was agitated at room temperature for 16 hrs during which time the methylene chloride was evaporated. The solid microspheres were allowed to settle and the aqueous phase that contained the polymeric dispersing agent was replaced by distilled water using at least five washings and decantation steps. The microspheres were isolated by filtration, washed, eventually sieved (20 mesh) and dried overnight at 37°C. It should be emphasized that the entire manufacturing process was protected as much as possible from light. Duplicate batches were prepared for reproducibility evaluation. The following preparation parameters were varied: the volume of the organic solvent phase, rate of agitation and nifedipine concentration. The empty Eudragit microspheres were prepared using identical experimental conditions but in the absence of nifedipine.

Microsphere evaluation

Nifedipine content

Known amount of nifedipine microspheres (20-100 mg) were dissolved in 50-100 ml of chloroform (analytical grade). Nifedipine was then assayed spectrophotometrically using a calibration curve at 338 nm. The dissolved Eudragit polymers did not absorb at this wavelength. Actual or measured drug contents were usually lower than the theoretical values due to drug loss or partition to the aqueous phase during methylene chloride evaporation.

Microscopy studies

Optical and scanning electron microscopy were used to evaluate the drug incorporation and surface shape of the microspheres prepared under the various conditions. Particle size was determined using a Tiyoda microscope. Samples of microspheres (180-200) were dispersed on a slide and their diameter was then sized using suitable objectives.

Determination of methylene chloride traces

The assay was carried out using a Varian Gas Chromatograph (Model 5000 LC) under the following experimental conditions: the oven injector and flame ionization detector temperatures were 125 and 225°C respectively. A porapak column was used, the eluent was N_2 at a flow rate of 30ml/min and the injected volume 2 µl. Various concentrations of purified methylene chloride in purified methanol were injected (both solvents were distilled to discard any impurity which might interfere with the sensitive assay). Calibration curves were linear in the range of 50 to 500 ppm (the limit of detection was 10 ppm). The methylene chloride detection in the microspheres was performed by dissolving various amounts (20-200 mg) of microspheres in 20 ml of purified methanol prior to the injection.

Differential scanning calorimetry

Differential thermal analysis (heating cycles of 90-200°C) of the pure nifedipine, empty Eudragit microspheres and microspheres containing various amounts of nifedipine was carried out to evaluate the internal structure after drug incorporation. This was achieved by means of a Mettler TA 3000 system.

The microspheres were also evaluated for their release kinetic profiles and stability studies at three temperatures. These aspects will be discussed in detail in another, separate report.

RESULTS AND DISCUSSION

In the process of batch up-grading two main technical problems were identified based on research experience gained during previous work:

a. The agitation system and equipment selection.

b. The period of time at which methylene chloride should evaporate.

The approach used to resolve the various technical problems was based on the decision that the minimal amount of microspheres prepared per batch will be 25 gm.

a. The agitation system and equipment selection

It was previously shown that the formation of a stable emulsion of methylene chloride in water was vital for the successful formation of indivicual microspheres.[4,9] Two main factors played an important role in the emulsification of methylene chloride in water and influenced the microsphere size, the interfacial tension of the methylene chloride droplets in the surrounding aqueous phase and the forces of shear within the fluid mass. The former tends to resist the distortion of droplet shape necessary for fragmentation into smaller droplets whereas the latter forces act to distort and ultimately disrupt the droplets. The relationship between these forces largely determines the final size distribution of the methylene chloride in water emulsion which in turn controls the final size distribution of the solid microspheres formed.

Finally, the stirring system previously described was selected and was able to agitate efficiently 1L of PVA aqueous solution producing an axial flow accompanied by marked turbulence in the immediate vicinity of the impeller.

b. The methylene chloride evaporation process.

In the preparation of small batch production, methylene chloride was allowed to evaporate at room temperature. The entire process lasted for 75-90 min.[4] In the present study, the minimum volume of methylene chloride required to dissolve 25 g of Eudragit mixture (RS:RL; 1:1) was 60 ml. This volume was dispersed in 1 L of aqueous phase, however, because of the high viscosity of the organic solutions, it was very difficult to evaporate the methylene chloride within a few hours of mixing. Therefore, the emulsification temperature was raised to 40°C to effect the

methylene chloride evaporation in 3 hrs. The increase in temperature affected the microspheres which were accompanied by a significant amount of Eudragit debris instead of spherical microspheres. This should be attributed to the alteration of the protective effect of PVA which was probably sensitive to temperature variations. It was clear that microsphere formation should occur at room temperature. The use of optimal and efficient stirring conditions allowed for the evaporation of methylene chloride at room temperature, but more than 16 hrs were required to remove the organic solvent.

PVA acted as a protective polymer by being adsorbed at the oil/water interface of the droplets to produce a steric barrier which prevented the coalescence of the droplets. Therefore PVA formed a stable methylene chloride in water emulsion, even when nifedipine was dissolved in the methylene chloride phase. However, nifedipine tended to moderately crystallize spontaneously in the aqueous phase of the emulsion or on the surface of the microspheres when solvent evaporation approached completion. This nifedipine crystal formation was detected even at low drug payload of 5% (Fig 1). Most of the free drug crystals that formed either floated in the water phase or were so loosely attached to the microspheres that they washed off during the isolation step. The loss of free drug crystals reduced the amount of nifedipine incorporated in the microspheres. Measured drug contents were always relatively high. Large amounts of nifedipine were not partitioned from the methylene chloride phase into the aqueous phase during the multihour fabrication process. This would account for the reduction in loss rate with increasing initial concentration of nifedipine as observed.

Methylene chloride residual in the microspheres

Nifedipine microspheres having a payload of either 4.6 or 31% (w/w) were stored at 4,20 and 37°C and were examined for methylene chloride residue. No methylene chloride peak could be detected (10 ppm limit of detection) following dissolution in purified methanol and injection of 2 µl in the gas chromatograph. Identical results

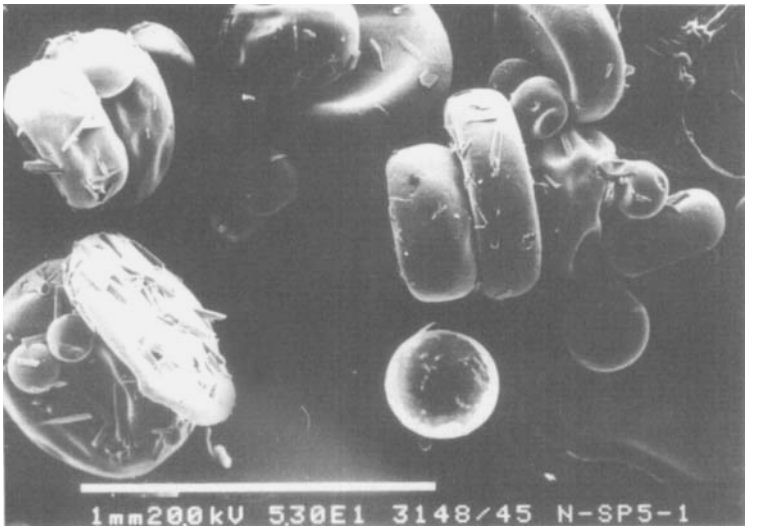


FIGURE 1
Scanning electron micrograph of nifedipine-loaded microspheres (4.7% w/w) prepared using 1L of 0.8% polyvinyl alcohol solution, 25 g Eudragit mixture RS:RL (1:1) in 80 mL methylene chloride stirred at 400 rpm.

were obtained for the microspheres stored at various temperatures indicating that effective removal of volatile solvent occurred following the separation and isolation process and before microsphere storage. From these results it can be concluded that less than 0.1% (v/w) methylene chloride is present in the solid microspheres calculated on the dried basis.

Differential scanning calorimetry analysis

This analytical method characterizes the nature of the drug encapsulated in the microspheres. The present study of nifedipine microspheres revealed no thermal event during the examination of empty microspheres. However, in the case of the melting phase transition of pure nifedipine, a sharp endotherm was observed at 172-3°C, corresponding exactly to the melting point of nifedipine (Fig 2A) whereas no thermal event at all was detected in the microspheres containing 4.7% (w/w) nifedipine (Fig 2B). The

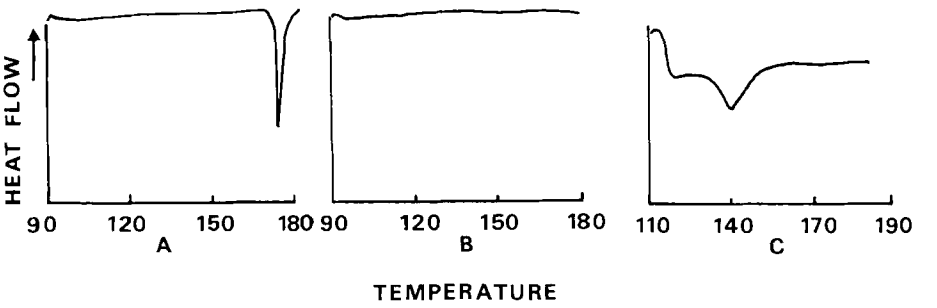


FIGURE 2
Differential thermal calorimetry analysis of pure nifedipine (A), Eudragit microspheres containing 4.7% nifedipine (B) or 31% nifedipine (C).

thermal behaviour of these nifedipine microspheres was similar to that observed with empty Eudragit microspheres.

It can therefore be deduced from these results that nifedipine at this concentration in the Eudragit microspheres was present either in a molecular dispersion or a solid solution state.

This was also confirmed by the SEM analysis. It can be seen from Figs 1 and 3, that microspheres containing up to 5% nifedipine had very smooth surfaces. There was no evidence of macroscopic pores. Formation of nifedipine fine crystals seemed to have no effect on the surface structure of the nifedipine microspheres when the drug payload was 4.8% (w/w). However, these microspheres did not appear totally spherical.

The nifedipine-loaded microspheres with a drug payload of 31% had a clear inflection at 139.6°C which should be attributed to the presence of crystalline domains in the microspheres (Fig 2C). This peak was not close to the melting point of pure nifedipine, indicating that during the methylene chloride evaporation phase, no recrystallization of pure nifedipine occurred within the microspheres, probably as a result of molecular interactions between nifedipine and the Eudragit polymers. Nevertheless, this

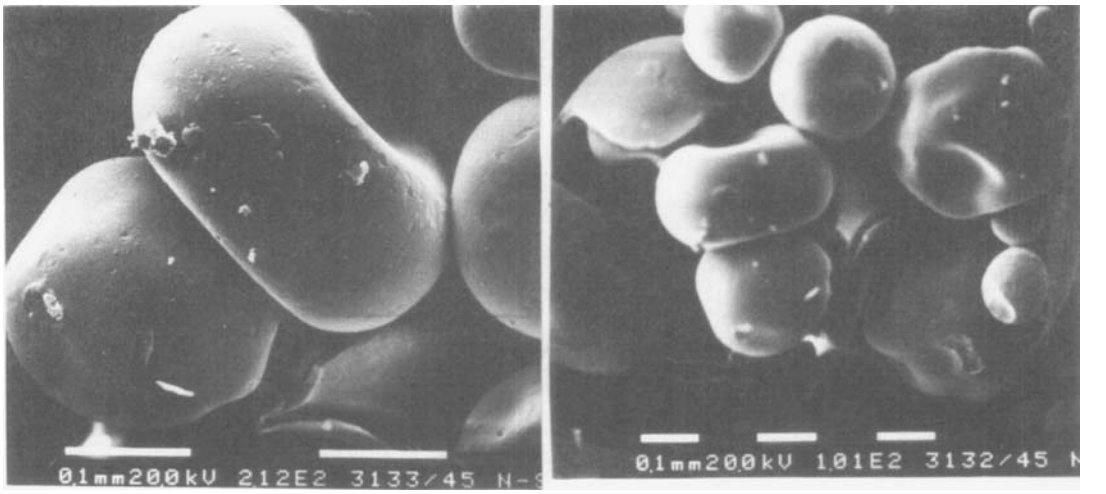


FIGURE 3

Scanning electron micrograph of well-washed nifedipine- loaded microspheres (4.7% w/w) at various magnifications. For experimental conditions see Fig 1.

inflection provided evidence that at least some of the nifedipine existed in the microsphere in a solid state. This evidence is consistent with the SEM examinations, which indicated that drug crystals were embedded on the microsphere surfaces (Fig 4). It could be noted from Fig 4, that the microspheres were not quite spherical and some of them, especially the large microspheres, collapsed and lost their spherical shape due to the existence of internal void volume as evidenced by Fig 5, exhibiting the internal structure of a fractured nifedipine microsphere having a payload of 31%. This morphological depression states should be attributed to the method used to prepare the microspheres for SEM evaluation. To visualize the microsphere, in SEM, a gold coating is imparted. During the gold coating process, the nifedipine microspheres which may comprize internal void volumes may probably become deflated by the vacuums required to carry out the coating

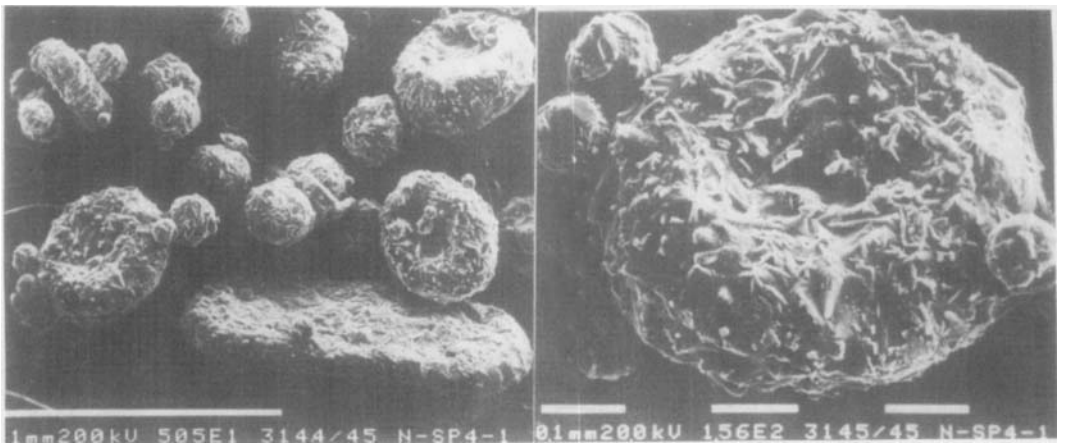


FIGURE 4
Scanning electron micrograph of nifedipine-loaded microspheres (31% w/w) at various magnifications. For experimental conditions see Fig 1.

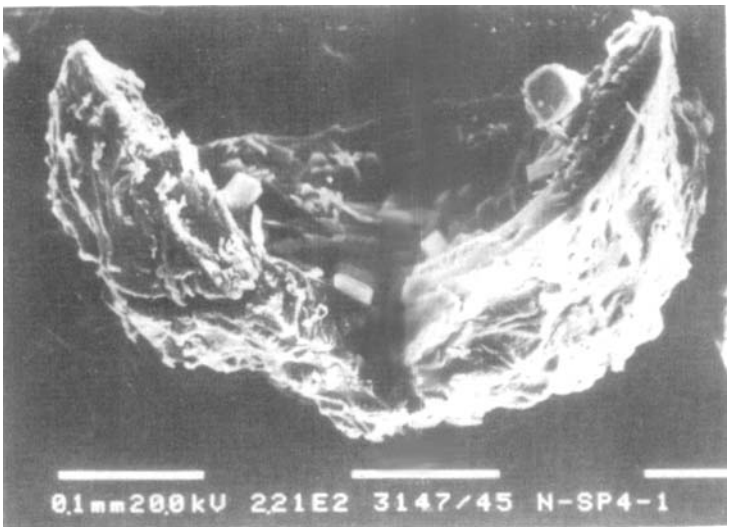
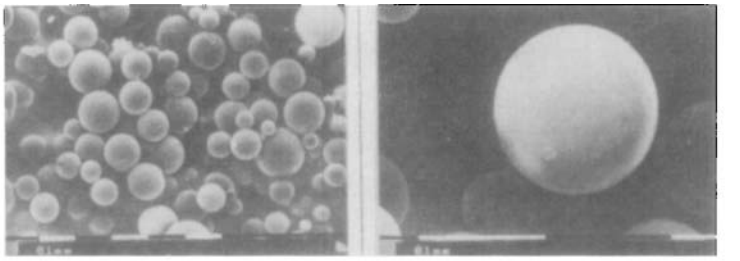
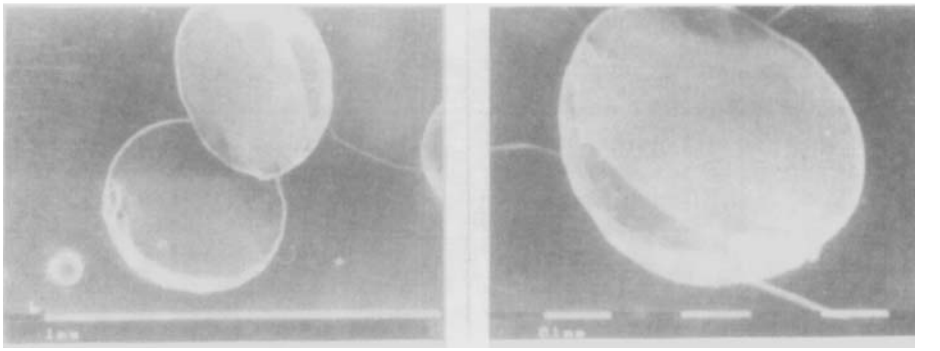


FIGURE 5
Scanning electron micrograph of a fractured nifedipine-loaded microsphere (31% w/w).



A



B

FIGURE 6
Scanning electron micrograph of nifedipine-loaded microspheres (5% w/w) (A) and cross-sectional view of nifedipine loaded microspheres (17% w/w) (B) prepared on a small laboratory scale not exceeding 2.5 g total microsphere amount per batch.

process. This should account for the various wall collapses detected by SEM. Nevertheless, rehydration of the microspheres regenerated their spherical shape, as observed by means of an optical microscope. It is interesting to note that a microsphere preparation method based on solvent evaporation process did not produce dense micromatrices as previously reported [4]. It should be emphasized that when the nifedipine microspheres were prepared using identical experimental conditions but on a small laboratory scale not exceeding 2.5 g total microsphere amount per batch, dense, homogeneous, spherical micromatrices with the nifedipine either molecularly dispersed or dissolved in the polymer were obtained (Figs 6A & B). The batch upgrading process has

TABLE 1
EFFECT OF INITIAL METHYLENE CHLORIDE VISCOSITY ON THE NIFEDIPINE MICROSPHERE CONTENT

Methylene chloride phase volume (ml)	Measured drug content (%)		Drug loss (%)[a]	
	Batch 1	Batch 2	Batch 1	Batch 2
60	8.7	7.1	4.4	22
70	8.4	7.0	7.7	23
80	8.5	7.9	6.6	13.2
100	7.7	7.2	13.4	19

All the Eudragit microspheres (RS:RL; 1:1) had a theoretical content of 9.1% w/w nifedipine and were made by the evaporation process with 0.8% polyvinyl alcohol as the emulsifier at 600 rpm.

[a] $\frac{[\text{Theoretical drug content} - \text{measured drug content}]}{\text{Theoretical drug content}} \times 100$

therefore led to the formation of nifedipine loaded microspheres with different morphological properties. However, in no case could these microspheres be defined as microcapsules, since there is no distinct core material (nifedipine) which is enclosed in the membranic envelope.

Effect of methylene chloride phase viscosity

The viscosity of the emulsified organic solvent phase was increased by reducing the volume of methylene chloride needed to dissolve 25 g of Eudragit mixture and 2.5 g of nifedipine. It could be seen from the results reported in Table 1, that the interbatch reproducibility was affected by the variation of the initial organic phase viscosity although no marked difference in measured drug payloads was observed with lower organic phase viscosities. Particle size frequency plot analysis of microsphere

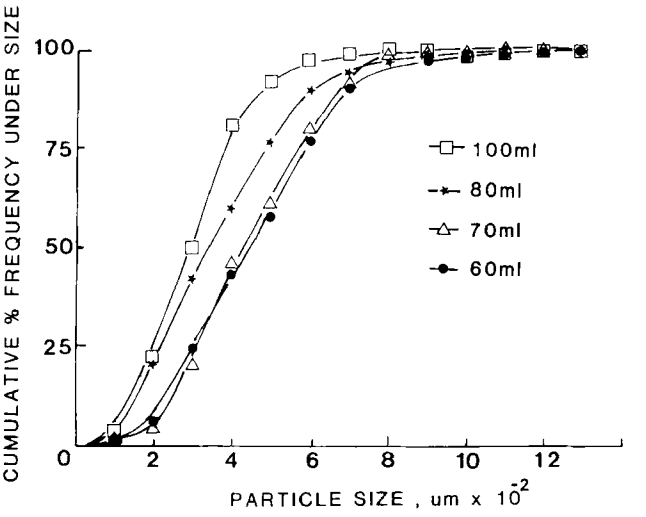


FIGURE 7
Cumulative frequency plot of nifedipine/Eudragit microspheres as a function of methylene chloride solution viscosity.

batches prepared with different volumes of methylene chloride revealed a moderate increase in particle size, with decreasing methylene chloride phase volumes from 100 to 70 ml (Fig 7). However, no marked difference could be observed between the populations of microspheres prepared using either 70 or 60 ml methylene chloride. Nevertheless, there was a clear tendency in mean measured diameter increase of the microspheres with decreasing methylene chloride phase volume. 289±119, 383±183, 432±134 and 450±175 m for methylene chloride phase volumes of 100, 80, 70 and 60 ml respectively. The increase in particle size should be attributed to the increase in the methylene chloride phase viscosity caused by the diminution of the solvent volume which yielded larger emulsified droplets and consequently larger solid microspheres.

Effect of stirring rate

As expected, increasing the stirring rate decreased the mean diameter of the microspheres (Table 2). It was also observed that

TABLE 2
EFFECT OF STIRRING RATE ON NIFEDIPINE MICROSPHERE CONTENT AND SIZE

Stirring rate (rpm)	Measured drug content (%)		Drug[a] loss (%)		Mean particle size m SD	
	Batch 1	Batch 2	Batch 1	Batch 2	Batch 1	Batch 2
200	6.8	6.5	25.3	28.6	567±302	780±304[b]
400	6.8	7.9	25.3	13.2	436±203	463±145
600	8.5	7.9	6.6	13.2	383±183	386±104
750	8.6	8.2	5.5	9.9	307±107	305±151

All Eudragit microspheres (RS:RL; 1:1) had a theoretical content of 9.1% w/w nifedipine and were prepared using 25 g of Eudragit mixture and 2.5 g of nifedipine dissolved in 80 mL initial methylene chloride volume phase.

[a] as in Table 1
[b] A large proportion of the microspheres were elongated.

the range of particle size obtained is close to the range required for a multiparticulate dosage form. It should be noted that the width of the size distribution as reflected by the value of SD did not show any tendency with increasing stirring rate. Nevertheless, sieving could be performed in cases where a narrow range of microspheres is needed.

It also appears that stirring rate might affect the drug incorporation efficiency in the microspheres since less drug losses were observed with increasing agitation rate (Table 2). With regard to batch reproducibility, either in drug content or mean particle size, no marked difference was observed between the two batches prepared under identical experimental conditions, although some discrepancy was noted in the drug payload of the microspheres prepared using a stirring rate of 400 rpm.

TABLE 3:
EFFECT OF INITIAL NIFEDIPINE CONCENTRATION ON MICROSPHERE DRUG CONTENT*

Initial nifedipine concentration % w/w	Measured drug[b] content (%)	Drug loss (%)[a]
4.8	4.6	3.5
9.1	7.4	19.2
16.6	14.3	14.0
23.0	18.8	18.4
33.3	31.1	6.6

* Microspheres were prepared using 1 L of 0.8% polyvinyl alcohol solution, 25 g of Eudragit mixture RS:RL (1:1) in 80 mL of methylene chloride stirred at 400 rpm.

[a] as in Table 1; [b] mean values of duplicates.

Effect of initial drug concentration

In an attempt to increase the nifedipine content of the microspheres, a number of experiments with increasing amounts of nifedipine were performed. The data reported in Table 3 showed that high payloads were achieved indicating that no rejection of nifedipine due to molecular interactions with the Eudragit polymers occurred. With regard to drug losses, no clear tendency was noted since drug loss values fluctuated with initial nifedipine concentration variation (Table 3).

It was also observed that increasing the nifedipine content in the microsphere altered the morphology of the microspheres (Figs 3,4). Clear findings were noted in the extreme cases, i.e., drug payloads of 4-8% or 31% w/w, but no clear conclusion could be drawn from the SEM observations of nifedipine microspheres having payloads from 10% to 25% w/w (Fig 8 A and B). In contrast to the low nifedipine loaded microspheres (4.8% w/w), which exhibited smooth surfaces, in these intermediate payloads formation of free

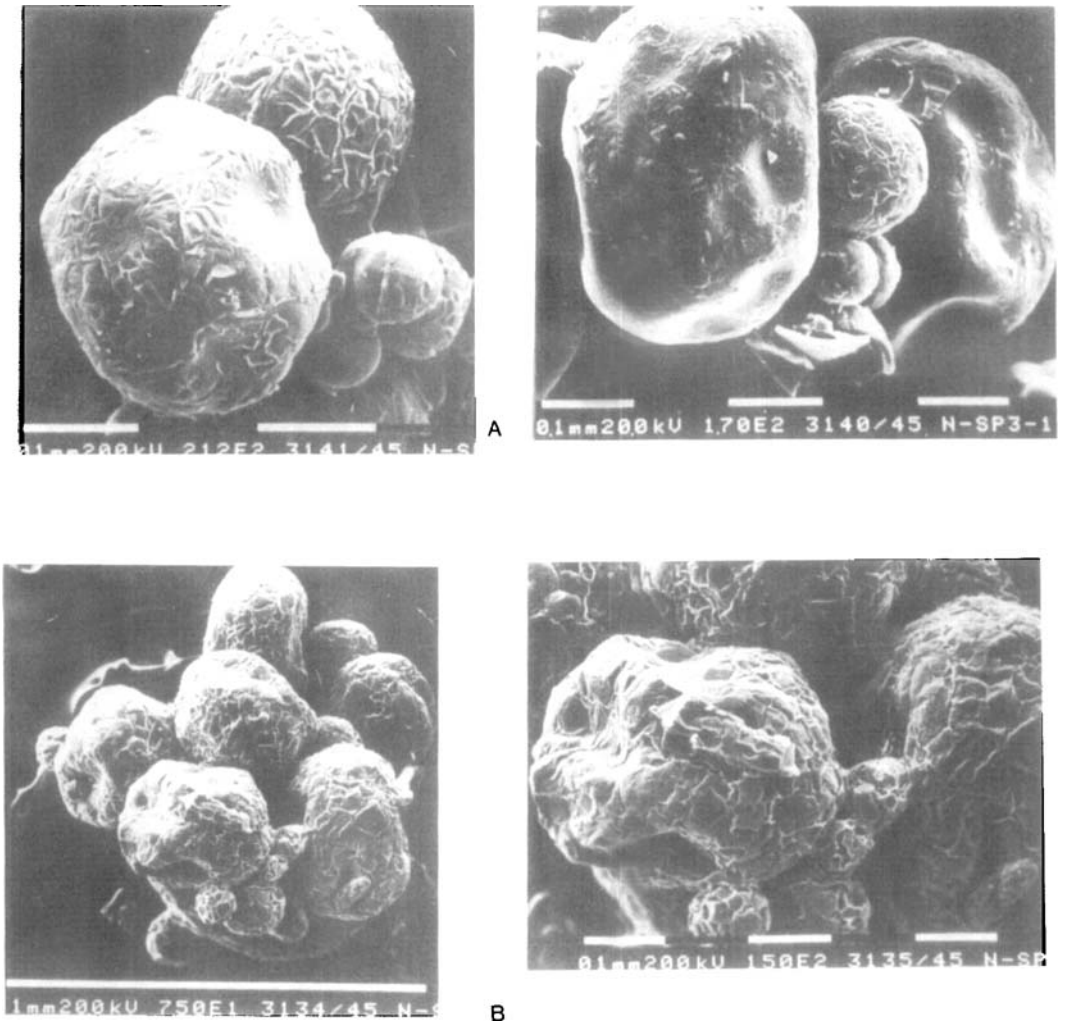


FIGURE 8
Scanning electron micrograph of Eudragit microspheres containing 14.3% nifedipine (A) and 18.8% nifedipine (B) at various magnifications. For experimental conditions see Fig 1.

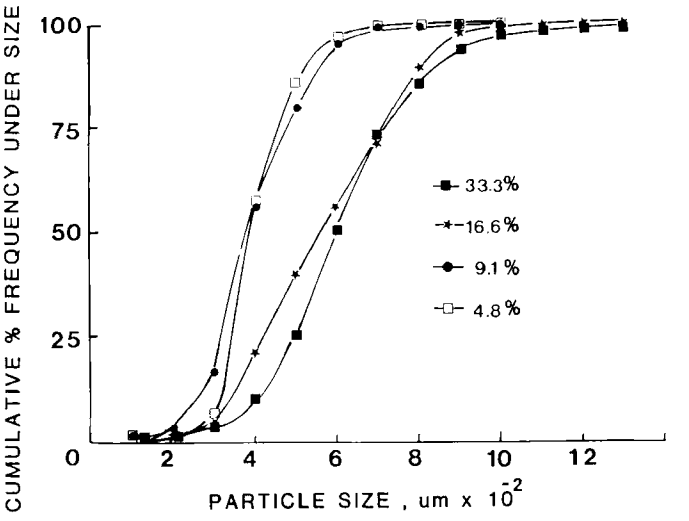


FIGURE 9
Cumulative frequency plot of nifedipine/Eudragit microspheres as a function of the initial nifedipine concentration. Microspheres were prepared using 1L of 0.8% PVA, 25g of Eudragit mixture RS:RL (1:1) in 80 ml of methylene chloride stirred at 400 rpm.

nifedipine crystals probably affected the surface structure of the nifedipine microsphere which showed rippled and rough surface (Fig 8A & B). Nor were nifedipine crystals observed attached firmly to the surface structure of the nifedipine microspheres. Thus, this phenomenon should rather be attributed to possible molecular interactions between the coating polymer and the nifedipine that to an excess of incorporated drug which might result in recrystallization of nifedipine within the microspheres. This was further supported by the lack of any thermal event during the differential scanning calorimetry analysis of these microspheres (discussed previously).

With respect to mean and particle size distribution, incorporation of increasing amounts of nifedipine within the microspheres gradually augmented their mean diameter and particle size distribution as shown in Fig 9. It could be observed that in

spite of a large degree of overlap in the particle size of the microspheres prepared using either the low or the high initial drug concentration, there was a clear tendency towards particle size increase with increasing nifedipine concentration. A similar behaviour was noted in the respective calculated mean diameters: 397 ± 92, 386 ± 104 μm for microspheres with drug content of 4.8 and 9.1 % respectively, 546 ± 201 and 599 ± 183 μm for nifedipine loaded micropheres having payloads of 16.6 and 31% (w/w) respectivey.

CONCLUSION

It appeared that the experimental conditions used in the present study favoured the formation of microspheres of a new type which could be defined as "film-type" micropspheres. They consisted of spherical micromatrices comprising an internal void space and a polymeric membrane of variable thickness where the drug is dispersed either in a molecular or solid state depending on the payload extent.

ACKNOWLEDGMENTS

The authors would like to acknowledge the support given by Roehm Pharma, Darmstadt, FRG.

REFERENCES

1. K.O.R. Lehman and D.K. Dreher, Pharmaceutical Technology, 3, 5 (1979).

2. S. Benita, A. Hoffman and M. Donbrow, J. Pharm. Pharmacol., 37, 391 (1985).

3. M. Donbrow, S. Benita and A. Hoffman, Applied Biochemistry and Biotechnology, 10, 245 (1984).

4. D. Babay, A. Hoffman and S. Benita, Biomaterials, 9, 255 (1988).

5. A.M. Fouili, A.A. Sayed and A.A. Bodawi, Internl. J. Pharm., 14, 95 (1983).

6. E.M. Ramadan, A. El-Helw and Y. El-Said, J. Microencapsulation, 5, 125 (1988).

7. M. Kawata, S. Nakamura, S. Goto and T. Aoyama, Chem. Pharm. Bull., 34, 2618 (1986).

8. Y. Pongpaibul, J.C. Price and C.W. Whitworth, Drug Devel. Ind. Pharm., 10, 1597 (1984).

9. Sawaya, A., Benoit, J.P. and Benita, S., J.Pharm. Sci., 76, 475 (1987).

10. S. Benita, J.P. Benoit, F. Puisieux and C. Thies, J. Pharm. Sci., 73, 1721 (1984).