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# Nifedipine loaded-polymeric microspheres: preparation and physical characteristics

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**Abstract**

Nifedipine-loaded microspheres of cellulosic polymers were prepared by a solvent evaporation method. The goal of this work was to investigate the influence of some process parameters on the physical characteristics of microspheres (size, drug content, kinetics of release). It appeared from obtained results that mean diameter of microspheres increased with the viscosity of the dispersed organic phase. Drug incorporation efficiency in ethylcellulose microspheres decreased when organic phase viscosity was increased. In the other hand, it was noted that drug loading efficiency could be enhanced by decreasing ethylcellulose/hydroxypropylcellulose (EC/HPC) or ethylcellulose/hydroxypropylmethylcellulose (EC/HPMC) ratios. Differential scanning calorimetry (DSC) thermograms and RX diffraction spectres indicated that nifedipine was incorporated in an amorphous state in the microspheres. All microspheres formulations exhibited slow and S-shaped release profiles with poor dissolution efficiency. However, release from microspheres of EC/HPC and EC/HPMC was slower but more regular than that from microspheres of EC (N10). It was also found that drug release was related to organic phase viscosity. Thus, in the case of EC, the higher was the viscosity of the organic phase, the slower was the release kinetic. Whatever the microspheres formulation, release patterns didn't exhibit any burst effect indicating the absence of free nifedipine or crystals on the surface of the microspheres. Nifedipine release from microspheres was well described by combined kinetics (zero- and first-order kinetics or zero-order and Higuchi square-roots kinetics). 

*Keywords:* DSC; Ethylcellulose; Microspheres; Nifedipine; X-ray diffraction; Zero-order release

## 1. Introduction

Nifedipine, a nitro-dihydropyridine and potent systemic calcium channel antagonist, is used in the treatment of angina pectoris and hyperten-

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sion. It is highly crystalline and poorly soluble in water. Its absorption, dissolution rate dependent, is low when administred orally in solid dosage forms (Kohri et al., 1987). On the other hand, nifedipine has a short elimination half-life leading to marked low plasma concentration following administration of conventional capsule form of nifedipine (Foster et al., 1983).

In order to improve the therapeutic efficiency of nifedipine, many authors have developped substained release formulations. Therefore, several ways have been explored: hydroxypropyl-$\beta$-cyclodextrin/hydroxypropylcellulose double layer tablets (Wang et al., 1993), alginate gel beads (Tateshita et al., 1993), chitosan microparticles (Chandy and Sharma, 1992; Filipovic-Grcic et al., 1996), poly (DL-lactide-co-glycolide) (PLGA) microspheres (Sansdrap and Moës, 1993; Sansdrap et al., 1995), Eudragit microparticles (Barkai et al., 1990; Chowdary and Girija Sankar, 1997) and albumin microspheres (Chuo et al., 1996).

The aim of this work was to prepare nifedipine-loaded ethylcellulose (EC) microspheres and to evaluate the influence of EC viscosity, drug/EC ratio and EC/water soluble polymers associations on the physical characteristics of the microspheres using X-ray analysis, DSC analysis and in vitro dissolution test. Two water soluble polymers have been associated with EC hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC) in order to adjust the water permeability of EC and so attempt to achieve a zero order release of nifedipine over 24 h.

With the intention of defining the experimental conditions for the preparation of microspheres, a preliminary study was carried out.

## 2. Materials and methods

### 2.1. Materials

Nifedipine was synthetized by the classical three-component Hantzsch reaction (at the Laboratoire de Chimie Thérapeutique of Université de Bordeaux 2) (Loev et al., 1974; Varache-Lembège et al., 1996).

Ethylcellulose (EC) of different viscosities (Hercules/Aqualon, France), hydroxypropylmethylcellulose (HPMC) (Methocel E50LV, Colorcon, UK) and hydroxypropylcellulose (HPC) (Klucel EF; Aqualon, France) were kindly supplied and used as received. The EC (EC N4, EC N10, EC N22, EC N50) had an ethoxyl content of 48.4–48.9% w/w and a viscosity of 5, 9, 19 and 51 cps, respectively (viscosity of 5% w/w solution in a solvent mixture of 80:20 w/w toluene/ethanol was measured at 25°C on a sample dried 30 min at 100°C). Ten percent HPC aqueous solution and 2% HPMC aqueous solution had a nominal viscosity at 20°C of 200–600 and 50 cps, respectively. Polyvinyl alcohol (PVA; $M_w$ of 30000–70000) was obtained from Sigma (France) and sodium lauryl sulfate from Cooper (France). Dichloromethane (DCM) and methanol, analytical grade, were supplied respectively by Prolabo (France) and Carlo Erba (France).

### 2.2. Preparation of microspheres

Microspheres were prepared by a classical solvent emulsion evaporation method. Briefly, a fixed amount (1.8–1.5 g) of polymer (EC, EC/HPC or EC/HPMC) and nifedipine (0.2–0.5 g) were dissolved in 20 ml of DCM or 4:1 (v/v) DCM/methanol mixture for EC/HPMC blends. The prepared clear organic solution was then added at room temperature, under constant mechanical stirring (500 rpm) (electronic Heidolph stirrer), to 160 ml of 0.45% (w/w) PVA aqueous solution, in a 400 ml glass becker installed in a thermostatic water bath. Agitation was then continued over 15 min before increasing the temperature to 37°C until complete evaporation of DCM (140 mn). The stirring system was able to agitate efficiently the aqueous solution producing an axial flow accompanied by marked turbulence in the immediate vicinity of the impeller. Higher temperatures decreased the DCM evaporation process time, but affected the integrity of the microspheres resulting in EC debris formation instead of spherical microspheres, due to alteration of the PVA prospective effect (Barkai et al., 1990). The solid micropheres were washed with 50 ml of desionized water (at least five washing and decan-

tation steps). The microspheres were isolated on a glass sintered filter (15 $\mu$m) and freeze dried for 24 h. Then microspheres were sieved (90 $\mu$m).

Empty microspheres were prepared using identical experimental conditions but in the absence of nifedipine.

Nifedipine undergoes photodegradation to dehydronifedipine upon exposure to ultraviolet light and to the nitroso analogue of dehydronifedipine when exposed to sunlight. These photodegradation products do not contribute to the clinical activity (Grundy et al., 1994). Since nifedipine is photosensitive in nature, all experiments were carried out in a darkroom.

### 2.3. Physicochemical determinations of the interaction

#### 2.3.1. Viscosity measurement

The viscosity of the organic phase was measured at 19°C using a Brookfield DVII + viscosimeter (Brookfield Englabs, USA) with RV 4 spindle at 100 rpm after 30 s.

#### 2.3.2. Size distribution of microspheres

Particle mean size, size distribution and surface shape were determined by means of a microscopical imaging analysis technique (Olympus BX40 microscope linked to Sony black and white monitor). Sample of microspheres were dispersed on a slide and the diameter of 150 U was then sized at random and surface shape looked using suitable objective. Each determination was carried out on two samples.

#### 2.3.3. Determination of drug content

A sample of 25 mg of nifedipine microspheres was dissolved in 500 ml of (3:2) ethanol:water mixture. The drug content of microspheres was determined spectrophotometrically ($\lambda$:237 nm) using a calibration curve. In these conditions, used polymers do not interfer with nifedipine absorption.

#### 2.3.4. X-ray analysis

The physical state of nifedipine in its various preparations was explored by X-ray diffraction. Powder X-ray diffractometry was carried out with a Siemens X-ray diffractometer (D500) using Ni-filtered, $CuK_{\alpha}$ radiation ($\lambda = 1.5418$ Å), a voltage of 40 kV and a current of 40 mA. The scanning rate was 0.06°/min over a $2\theta$ range of 3–40°.

#### 2.3.5. DSC

Thermal analysis was performed using a Mettler TA 4000 system with a differential scanning calorimeter equiped with a computerized data station (Mettler DSC 30, Mettler-Toledo AG, Switzerland).

All samples were weighted and heated at scanning rate of 10°C/min between 30 and 270°C. Aluminium pans and lids were used and temperature calibrations were performed periodically using indium as standard.

To evaluate the internal structure modifications after drug incorporation, analysis was performed on pure substances, physical mixture of polymers and nifedipine, empty and nifedipine-loaded microspheres.

### 2.4. In vitro dissolution studies

Dissolution studies were performed using USP XXIII apparatus (rotating paddle method; dissolution apparatus Sotax model AT7, Switzerland). Samples of pure drug and nifedipine loaded microspheres (equivalent to 10 mg of nifedipine) were introduced in the dissolution medium (500 ml of 3% w/v sodium lauryl sulfate aqueous solution in desionized water). Phosphate buffers were discarded because nifedipine was found to be more soluble in water (Qureshi et al., 1994). The study was performed at 37°C with a stirring rate of 100 rpm. The dissolution medium was filterated through a 10 $\mu$m filter-fitted polypropylene tubing and continuously pumped (Watson Marlow 205U, UK) to flow cells (40 mm) in a UV double-beam spectrophotometer (Safas UV mc2, Safas Monaco), so that the absorbance was monitored automatically at 237 nm.

The dissolution tests were carried out for 24 h. The results were computed with a standard calibration curve of the drug ($r = 0.9992$). All experiments were carried out in triplicate.

Table 1
Different types of prepared nifedipine-loaded polymeric microspheres

| Name | Polymer(s) (EC/other polymer ratios) | Ratio drug/polymer | Viscosity of mixture dissolved in DCM[a] |
|---|---|---|---|
| Nif/EC4(1:9) | EC N4 | 1:9 | 48 |
| Nif/EC10(1:9) | EC N10 | 1:9 | 90 |
| Nif/EC22(1:9) | EC N22 | 1:9 | 292 |
| Nif/EC50(1:9) | EC N50 | 1:9 | 684 |
| Nif/EC10(1.5:8.5) | EC N10 | 1.5:8.5 | 82 |
| Nif/EC10(2:8) | EC N10 | 2:8 | 74 |
| Nif/EC10(2.5:7.5) | EC N10 | 2.5:7.5 | 66 |
| Nif/EC10/HPC(1:8:1) | EC N10/HPC (8:1) | 1:9 | 128 |
| Nif/EC10/HPC(1:7:2) | EC N10/HPC (7:2) | 1:9 | 188 |
| Nif/EC10/ HPMC(1:8:1) | EC N10/HPMC (8:1) | 1:9 | 72 |
| Nif/EC10/ HPMC(1:7:2) | EC N10/HPMC (7:2) | 1:9 | 94 |

[a] Viscosity (at 19°C) of nifedipine/polymers mixture dissolved in DCM before solvent evaporation.

### *2.5. Data and statistical analysis*

Statistical evaluations were performed using a Student's $t$-test and a one-way analysis of variance (ANOVA) using a statistical package Statview (Abacus Concepts, CA). Bonferroni test was employed after ANOVA to evaluate statistical differences between individual means, since it permitted a comparison of multiple results and isolation of the sources of significant differences. In all cases $p < 0.05$ was accepted to denote significance.

## 3. Results and discussion

The goal of this study was the development of a sustained release system for nifedipine. Microspheres were prepared by solvent evaporation. The effects of three process variables namely polymer nature, polymer viscosity and nifedipine/polymer ratio on the microspheres characteristics (size, entrapment efficiency of drug and nifedipine release rate) were explored. Eleven microsphere formulations were prepared and are listed in Table 1.

The viscosity of the organic phase (polymer + nifedipine + DCM) was measured. As can be seen in Table 1, viscosity of the organic phase increased as the ethoxyl content of EC increased. On the other hand, the viscosity decreased as the drug/EC ratio increased and EC/HPC or EC/HPMC ratios decreased. The poor viscosity in the presence of HPMC as compared with EC (N10) could be explained by the dilution of the organic phase with 5 ml of methanol.

Table 2 shows the main properties of different types of microspheres. Microspheres prepared using EC were found to be spherical, discrete, free flowing and of well-defined shape, whereas, EC/HPC and EC/HPMC microspheres had less regular shape and held a HPC or HPMC lattice like.

The total microspheres recovered amount after 90 $\mu$m sieving varied between 69.0 and 80.6%. As EC viscosity increased, the microspheres yield decreased. A similar result was also obtained when HPC and HPMC were present in the microsphere formulations. Microspheres present a broad distribution and fall into the $117.17 \pm 32.14$ and $415.52 \pm 157.10$ $\mu$m size range. The size of the microspheres was influenced by EC viscosity. It could be observed that in spite of an overlap in the particle size of the microspheres, there was a clear tendency towards particle size increased with increasing EC viscosity (Fig. 1). So, microspheres with EC N50 exhibited the highest average diameter ($415.52 \pm 157.10$ $\mu$m). An increase in microspheres size was already reported (Barkai et al.,

Table 2
Characteristics of nifedipine-loaded polymeric microspheres (yield, average diameter of microspheres, incorporation efficiency of drug)

| Name | Yield (%) | Average diameter ± S.D. ($\mu$m) | Nifedipine incorporation efficiency (%) | Nifedipine content (%) |
|---|---|---|---|---|
| Nif/EC4(1:9) | 80.6 | 122.6 ± 27.11 | 93.52 | 9.35 |
| Nif/EC10(1:9) | 80.6 | 177.50 ± 35.33 | 87.22 | 8.72 |
| Nif/EC22(1:9) | 78.3 | 262.44 ± 66.21 | 85.54 | 8.55 |
| Nif/EC50(1:9) | 69.0 | 415.52 ± 157.10 | 79.61 | 7.96 |
| Nif/EC10(1.5:8.5) | 79.3 | 162.22 ± 37.08 | 88.47 | 13.27 |
| Nif/EC10(2:8) | 77.0 | 151.47 ± 26.16 | 84.88 | 16.98 |
| Nif/EC10(2.5:7.5) | 74.6 | 150.99 ± 24.30 | 87.84 | 21.96 |
| Nif/EC10/ HPC(1:8:1) | 65.2 | 117.17 ± 32.14 | 96.96 | 9.70 |
| Nif/EC10/ HPC(1:7:2) | 58.7 | 134.60 ± 45.40 | 106.56 | 10.66 |
| Nif/EC10/ HPMC(1:8:1) | 70.1 | 197.32 ± 68.34 | 90.21 | 9.02 |
| Nif/EC10/ HPMC(1:7:2) | 55.0 | 351.71 ± 126.38 | 100.92 | 10.09 |

Key (see Table 1).

1990) from nifedipine-loaded polyacrylate microspheres and attributed to the increase in the emulsified organic phase viscosity.

On the other hand, increase in the drug loading of EC 10 microspheres did not influence significantly either the mean diameter of microspheres or their size distribution (Fig. 1). Thus, when the drug/EC 10 ratio has been increased from 1:9 to 2.5:7.5, the mean diameter decreased only from 177.50 ± 35.33 to 150.99 ± 24.30 $\mu$m (Table 2) whereas the size distribution was pratically the same. Moreover, incorporation of HPC in the microspheres decreased their average diameter and inversely with HPMC. We don't have a plausible explanation for this.

The drug incorporation efficiency data reported in Table 2, showed that drug content of microspheres was higher than 79%. The difference between theoretical and measured values is likely to be due to the loss of nifedipine resulting from enhancement of its dissolution in water after it was dissolved with EC in DCM. In order to increase the drug content of microspheres, drug/polymer ratio was increased from 10 to 25% without significant plasticizing effect and hence a tacky formulation was noted. The data reported in Table 2 showed high payloads of nifedipine. This result indicated that rejection of drug due to molecular interactions with polymers did not occur. However, with regard to drug content of microspheres, one can see that there was no clear tendency since nifedipine content of microspheres fluctuated as the initial drug concentration in the organic phase varied. This result is in agreement with those reported by Barkai et al. (1990) in their work on polyacrylate microspheres.

The influence of EC viscosity on drug incorporation efficiency was studied. As polymer viscosity increased the percentage of drug loading decreased, but differences were not statistically significant. When HPC or HPMC were associated with EC 10, nifedipine entrapment efficiency was close or superior to the theoretical value. This is likely due, at least in part, to a possible migration of HPC or HPMC into the aqueous phase leading to an enhancement of drug/polymer ratio. This hypothesis is supported by the lower yield of microspheres obtained in the presence of HPC or HPMC in the microspheres formulations.

Fig. 2 showed the X-ray diffraction patterns of nifedipine, EC (N10), their physical mixture dissolved in DCM (after evaporation and grinding), and microspheres of nifedipine/EC N10. Nifedipine showed several peaks corresponding to the

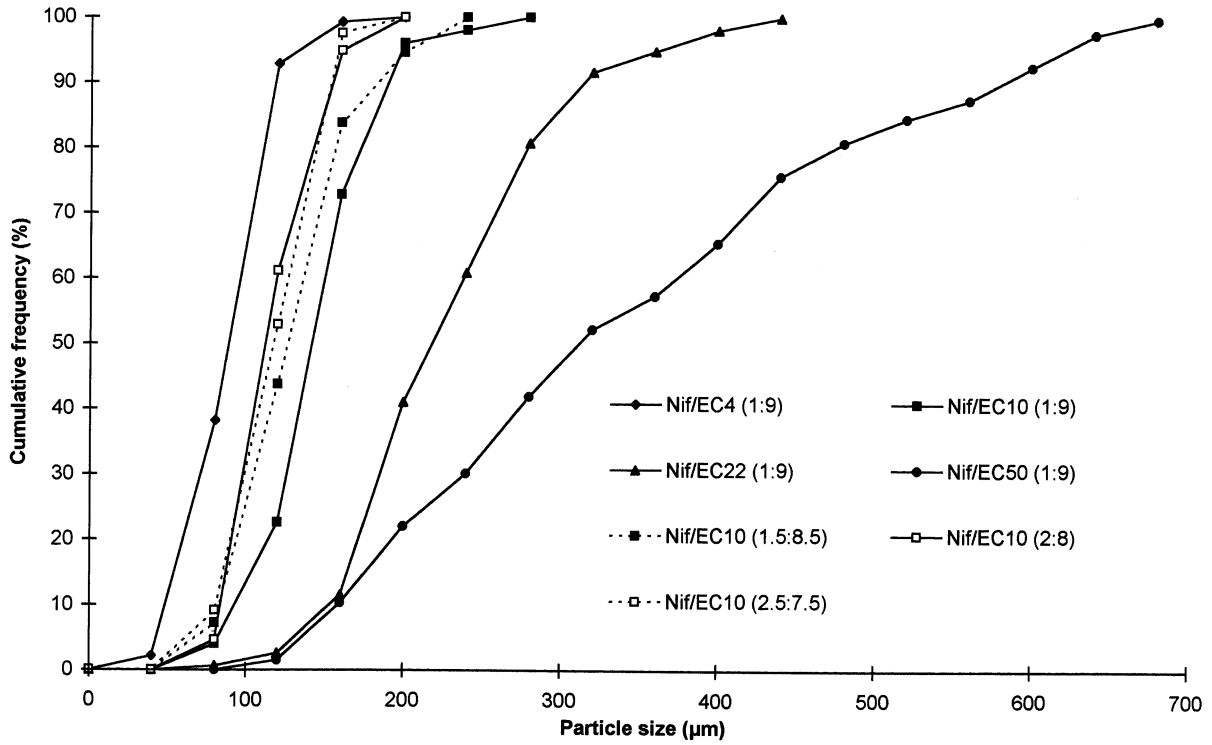


Fig. 1. Particle size distribution of different types of nifedipine-loaded polymeric microspheres. Key: Nif/EC4 (1:9) (nifedipine/ethylcellulose N4 (1:9) microspheres); Nif/EC10 (1:9) (nifedipine/EC N10 (1:9) microspheres); Nif/EC22 (1:9) (nifedipine/EC N22 (1:9) microspheres); Nif/EC50 (1:9) (nifedipine/EC N50 (1:9) microspheres); Nif/EC10 (1.5:8.5) (nifedipine/EC N10 (1.5:8.5) microspheres); Nif/EC10 (2:8) (nifedipine/EC N10 (2:8) microspheres); Nif/EC10 (2.5:7.5) (nifedipine/EC N10 (2.5:7.5) microspheres); Nif/EC10/HPC (1:8:1) (nifedipine/EC N10/hydroxypropylcellulose (1:8:1) microspheres); Nif/EC10/HPC (1:7:2) (nifedipine/EC N10/hydroxypropylcellulose (1:7:2) microspheres); Nif/EC10/HPMC (1:8:1) (nifedipine/EC N10/hydroxypropylmethylcellulose (1:8:1) microspheres); Nif/EC10/HPMC (1:7:2) (nifedipine/EC N10/hydroxypropylmethylcellulose (1:7:2) microspheres).

crystalline form while EC is mainly amorphous with a poor crystalline part. In contrast, samples of (nifedipine/EC N10) microspheres and nifedipine/EC N10 mixture after dissolution in DCM and evaporation (containing the same quantities of nifedipine and EC) showed a halo pattern in which diffraction peaks of drug have disappeared indicating that nifedipine in both preparations was in the amorphous state. These results proved that nifedipine and EC, after dissolution in DCM, produced after solvent evaporation of the solvent a solid dispersion in which the drug was dispersed in a molecular state. Similar results have been reported from Eudragit microspheres containing nicardipine hydrochloride (Yüksel et al., 1996) and Eudragit microcapsules of nifedipine (Chowdary and Girija Sankar, 1997).

Thermograms of pure materials (nifedipine and EC 10), physical mixture of nifedipine/EC before and after dissolution in DCM and evaporation, and drug-loaded microspheres are shown in Fig. 3. The other three types of EC and blends of EC/HPC or EC/HPMC, as well as their physical mixtures with nifedipine and their microspheres showed a similar thermal behaviour than EC 10, its physical mixtures with nifedipine and its microspheres, respectively. In the case of pure nifedipine, a sharp endotherm was observed at 173.7°C, corresponding to the melting point of nifedipine (172–174°C (Horster et al., 1972)). The end of the thermogram corresponded to break up of nifedipine (probably by decomposition). DSC analysis gives reliable information on the physico-

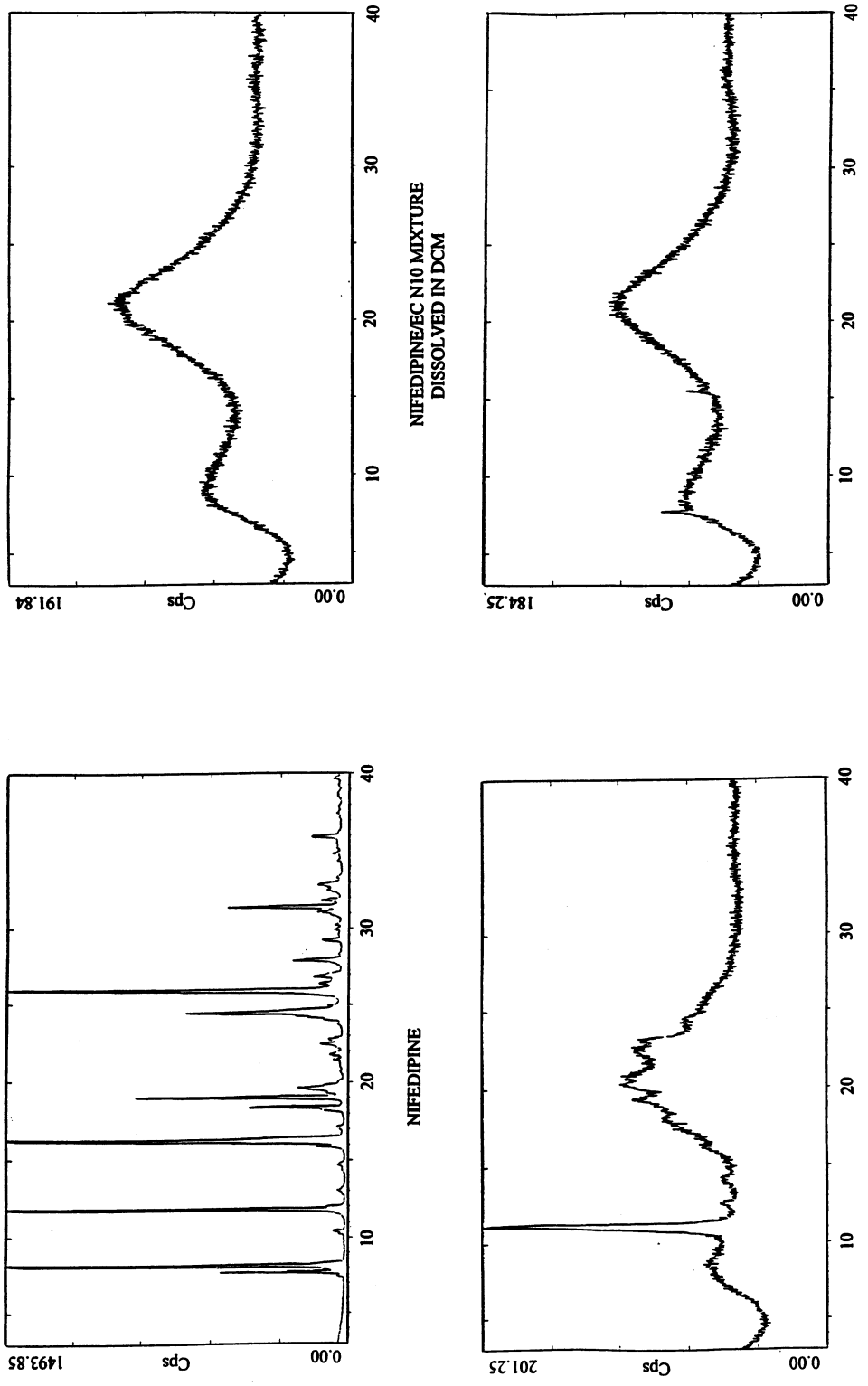


Fig. 2. Powder X-ray diffraction patterns of nifedipine, EC (N10), physical mixture nifedipine/EC (N10) after dissolution in DCM, evaporation and grinding, and microspheres of nifedipine/EC N10.

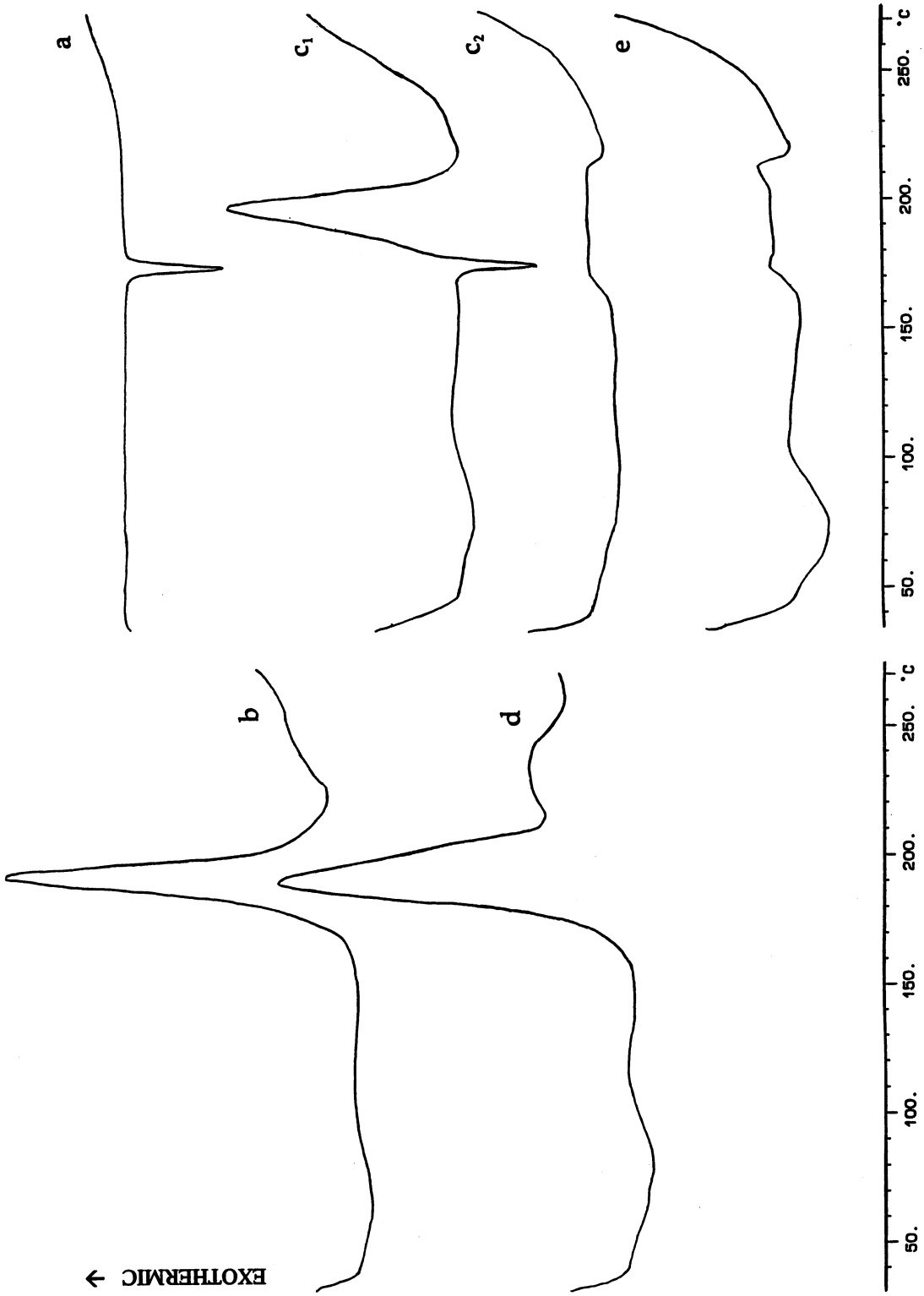


Fig. 3. DSC thermograms of (a) pure nifedipine, (b) ethylcellulose N10, ($c_1$) physical mixture of nifedipine and EC N10, ($c_2$) nifedipine/EC physical mixture after dissolution in DCM and evaporation, (d) empty EC (N10) and (e) EC N10 microspheres containing nifedipine.

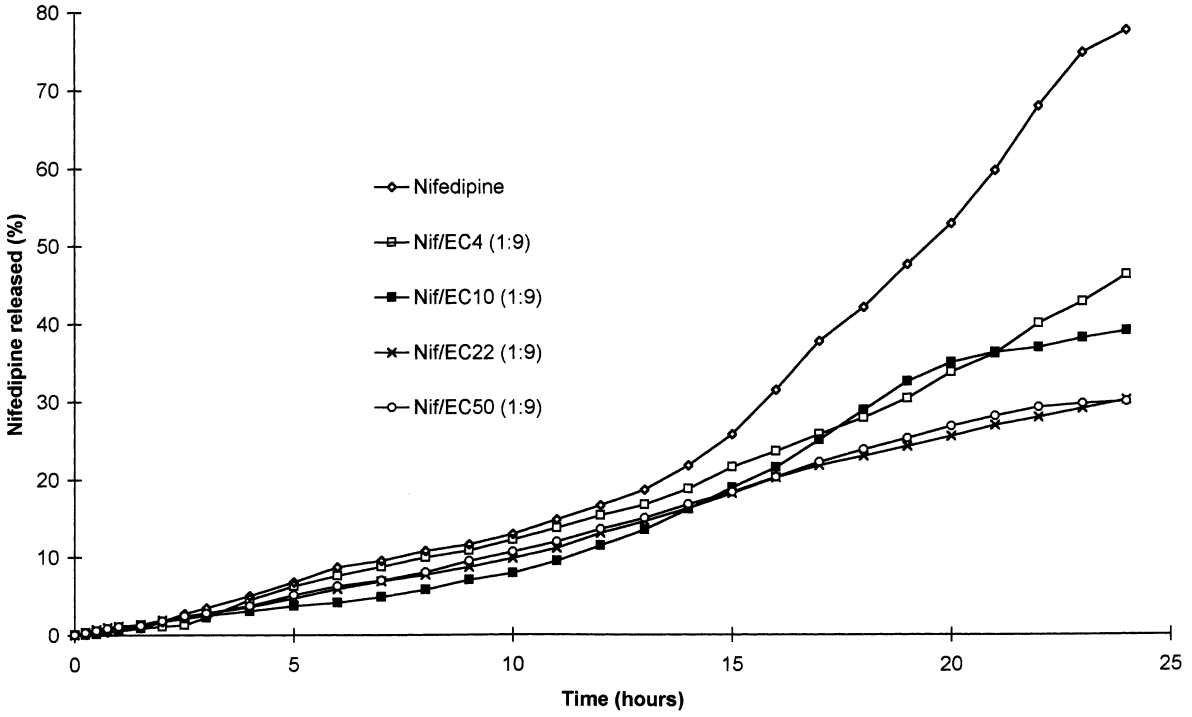


Fig. 4. In vitro nifedipine release profiles from pure drug and different types of nifedipine-loaded microspheres. Key: see Fig. 1.

chemical state of the ingredients of microspheres. Thus, DSC endotherms observed between 60 and 80°C for the raw materials and microspheres are attributed to the evaporation of the absorbed water. EC thermogram (bulk material) also display a large exothermic peak around 180°C resulting from oxydative degradation of the polymer. The examination of EC empty microspheres revealed an exotherm peak due to the melting point of EC (Fig. 3). The DSC curves of nifedipine/EC N10 physical mixture showed peaks resulting from simple superposition of their separated component DSC curves. In contrast, no endothermic peak corresponding to fusion of nifedipine was observed in the thermogram neither from nifedipine-loaded microspheres nor from nifedipine/EC physical mixture after dissolution and evaporation of DCM. The disappearance of the endothermic peak is due to the chemical interaction of the drug with EC N10. This can be explained by the complet dissolution of nifedipine crystals in the EC microspheres, i.e. the presence of nifedipine in an amorphous state, dissolved or molecularly dispersed in EC. Thus, X-ray results were confirmed by the DSC data. The existence of nifedipine in molecular state has been already reported by Chowdary and Girija Sankar (1997) in their work on nifedipine-loaded Eudragit microspheres. The thermogram of microspheres did not show inflection which should be attributed to presence of crystalline domain in the microspheres (i.e. nifedipine in particulate state dispersed in the polymeric matrix) as noted by Barkai et al. (1990) from Eudragit microspheres containing high concentration of nifedipine.

The cumulative drug release profiles from different types of nifedipine EC microspheres are shown in Fig. 4. Whatever the type of microspheres, no burst effect has been observed and all microspheres exhibited an S-shaped release pattern. It is clear that release rate of nifedipine from EC microspheres was slow and inversely related to polymer viscosity. Drug release from EC microspheres decreased with increasing of polymer

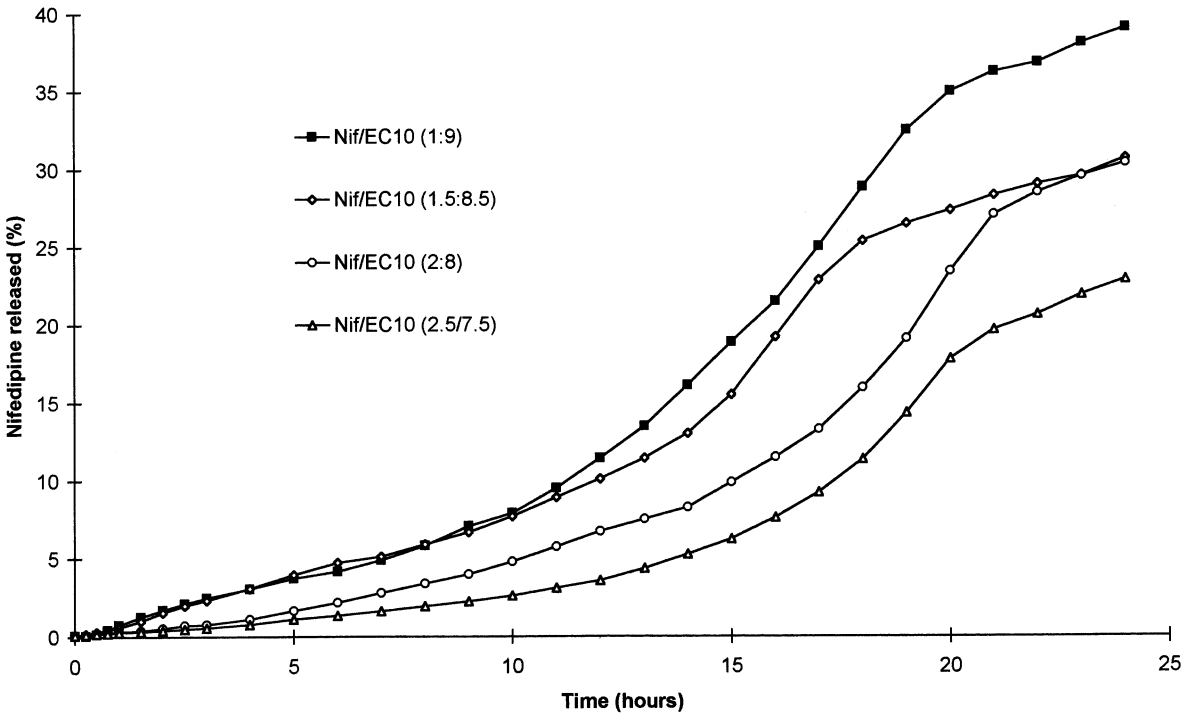


Fig. 5. In vitro release profile of nifedipine from EC (N10) microspheres with different nifedipine/EC ratios. Key: see Fig. 1.

viscosity till a critical value equivalent to EC-N22 grade (18–20 cps: viscosity of 5% solution in 80:20 toluene/ethanol by weight) after that no further significant decrease was noted. This result is in agreement with those reported by Kristl et al. (1991) in their work on bacampicillin-loaded EC microcapsules and by Tefft and Friend (1993) in their investigation on herbicidal loaded EC microspheres. It must be noted that dependance of the liberation rate on viscosity or molecular weight of EC has already been reported by many authors like Deasy et al. (1980) and Rowe (1986).

The release rate of nifedipine from microspheres could also be related to the particle size as reported, for instance, by Sansdrap and Moës (1993) and Filipovic-Grcic et al. (1996). Small microspheres having very large surface area can provide massive release. In contrast, in our case, the size of the microspheres was large and the surface area was small so no burst effect could be observed. The release rate of nifedipine from EC N50 or EC N22 microspheres was found to be slower, but not statistically significant, as compared with EC N4 or EC N10 microspheres.

As it can be seen in Fig. 5 the rate of drug release was slightly influenced by the initial nifedipine loading and observed differences were not statistically significant. This is in good agreement with results reported by Thanoo et al. (1992) and Sansdrap and Moës (1993) but in contrast with findings of Filipovic-Grcic et al. (1996) in their work on nifedipine-loaded chitosan microspheres and Tefft and Friend (1993) from herbicide-loaded microspheres investigation.

Dissolution efficiency (DE) was determined from dissolution profiles of pure nifedipine and all types of microspheres (Table 3). It can be noted that DE values from microspheres remained very low as compared with pure drug. On the other hand, when EC was the only polymer used, the higher was the organic viscosity the lower was DE. In presence of HPC and HPMC DE increased as the organic phase viscosity increased. The description of dissolution profiles by a model

Table 3
Dissolution efficiency (DE) and correlation coefficient for linear relationship over 24 h release of zero-order, first-order, Higuchi, Hixson–Crowell, Rosin–Rammler–Serling–Weibull (Weibull) kinetics from different types of microspheres

| | Nifedipine | Nif/EC4 (1:9) | Nif/EC10 (1:9) | Nif/EC22 (1:9) | Nif/EC50 (1:9) | Nif/EC10 (1.5:8.5) | Nif/EC10 (2:8) | Nif/EC10 (2.5:7.5) | Nif/EC10/ HPC (1:8:1) | Nif/EC10/ HPC (1:7:2) | Nif/EC10/ HPMC (1:8:1) | Nif/EC10/ HPMC (1:7:2) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DE[a] | 25.90 | 18.05 | 16.03 | 14.16 | 14.66 | 3.52 | 10.15 | 7.07 | 9.81 | 11.00 | 7.86 | 9.98 |
| Zero-order | 0.948 | 0.985 | 0.969 | 0.995 | 0.996 | 0.976 | 0.937 | 0.916 | 0.982 | 0.991 | 0.979 | 0.985 |
| First-order | 0.912 | 0.900 | 0.898 | 0.888 | 0.880 | 0.913 | 0.949 | 0.983 | 0.921 | 0.840 | 0.879 | 0.885 |
| Higuchi model | 0.867 | 0.927 | 0.898 | 0.950 | 0.953 | 0.915 | 0.850 | 0.821 | 0.920 | 0.944 | 0.922 | 0.934 |
| Weibull model | 0.884 | 0.967 | 0.957 | 0.991 | 0.992 | 0.969 | 0.923 | 0.906 | 0.976 | 0.988 | 0.973 | 0.978 |
| Hixson–Crowell model | 0.909 | 0.974 | 0.961 | 0.993 | 0.993 | 0.972 | 0.928 | 0.910 | 0.978 | 0.989 | 0.975 | 0.980 |

[a] DE is defined as the area under the dissolution curve up to a certain time (here, 24 h) expressed as a percentage of the area of the rectangle described by 100% in the same time (Khan and Rhodes, 1972).

Table 4
Release constants ($a$) and correlation coefficients ($r$) for linear relationship of the proposed combined kinetics

| | Zero-order (0–10 h) | | Hixson–Crowell model (0–10 h) | | First-order (10–24 h) | | Higuchi model (10–24 h) | |
|---|---|---|---|---|---|---|---|---|
| | $a$ | $r$ | $a$ | $r$ | $a$ | $r$ | $a$ | $r$ |
| Nif/EC4 (1:9) | 1.30 | 0.991 | 0.021 | 0.990 | 0.04 | 0.998 | 19.53 | 0.984 |
| Nif/EC10 (1:9) | 0.76 | 0.996 | 0.012 | 0.995 | 0.05 | 0.970 | 20.28 | 0.990 |
| Nif/EC22 (1:9) | 0.96 | 0.999 | 0.015 | 0.998 | 0.03 | 0.975 | 12.07 | 0.969 |
| Nif/EC50 (1:9) | 1.05 | 0.998 | 0.017 | 0.997 | 0.03 | 0.978 | 12.17 | 0.996 |
| Nif/EC10 (1.5:8.5) | 0.76 | 0.999 | 0.012 | 0.999 | 0.05 | 0.960 | 15.08 | 0.982 |
| Nif/EC10 (2:8) | 0.45 | 0.984 | 0.007 | 0.983 | 0.06 | 0.992 | 16.53 | 0.965 |
| Nif/EC10 (2.5:7.5) | 0.24 | 0.990 | 0.004 | 0.990 | 0.07 | 0.990 | 13.15 | 0.967 |
| Nif/EC10/HPC (1:8:1) | 0.64 | 0.994 | 0.010 | 0.994 | 0.04 | 0.991 | 11.00 | 0.988 |
| Nif/EC10/HPC (1:7:2) | 0.73 | 0.998 | 0.012 | 0.997 | 0.04 | 0.965 | 9.73 | 0.987 |
| Nif/EC10/HPMC (1:8:1) | 0.46 | 0.976 | 0.007 | 0.977 | 0.04 | 0.969 | 7.86 | 0.978 |
| Nif/EC10/HPMC (1:7:2) | 0.67 | 0.982 | 0.011 | 0.983 | 0.04 | 0.998 | 9.53 | 0.982 |

function has been attempted using different kinetics (zero-order, first-order, Higuchi square-root model, Hixson–Crowell cube-root model, Weibull model and combinations). Correlation coefficients are reported in Table 3. As it can be seen, the entire release profiles of nifedipine from EC microspheres can not be simulated by any model properly since coefficients of correlation are not close to one. Then, description of the release patterns by the combine release kinetics has been tried. In Table 4 are presented the release constants and the coefficients of correlation for the proposed combined kinetics. It appears that in the first time (0–10 h), kinetic of release could be of zero-order since in most cases coefficient of correlation is close to one. However, the data also fit to Hixson–Crowell cube-root with nearly the same correlation coefficient values. Afterwards, Higuchi square-root becomes the most appropriate model to describe kinetics. However, it is more likely that phase 2 resulted also from two or more combined kinetics. Coefficients of correlation exhibit in most cases higher values for combined kinetics (Table 4) than for proper models (Table 3). Similar results have been already reported for microcapsules (Benita and Donbrow, 1982; Kristl et al., 1991). A possible explanation for the combine kinetics is to assume that in the beginning (0–10 h), the drug release was only dependent of the microspheres hydration rate. When the microspheres were completely hydrated (10–24 h), release of nifedipine increased and followed Higuchi square-root model. The complete absence of the burst effect allows to demonstrate the absence of nifedipine crystals on the surface of all types of EC microspheres and corroborates our DSC and light microscopy results. Thus, it is proposed that nifedipine is entirely and uniformly incorporated, in molecular form, in the microspheres. The rate of release is then controlled by the permeability of the matrice structure.

The nifedipine release profiles from EC/HPC and EC/HPMC microspheres did not exhibit, any burst effect (Fig. 6). HPC and HPMC were added to EC in microspheres formulations with intent to make drug release kinetic closer to zero-order over a 24 h period time than that obtained from EC microspheres by adjusting the water permeability of the water insoluble polymer (EC). Blends of water-soluble and water-insoluble polymers were already used in the development of multiparticulate dosage forms and films for controlled release of drugs (Donbrow and Friedman, 1975; Roy et al., 1992). The release rate of nifedipine increased with increasing of HPC /EC and HPMC/EC ratios. It was closer to zero-order but remained slower as compared with release from EC microspheres. This result is in agreement with that reported by Roy et al. (1992) from the investigation on indomethacin-loaded EC/methyl-

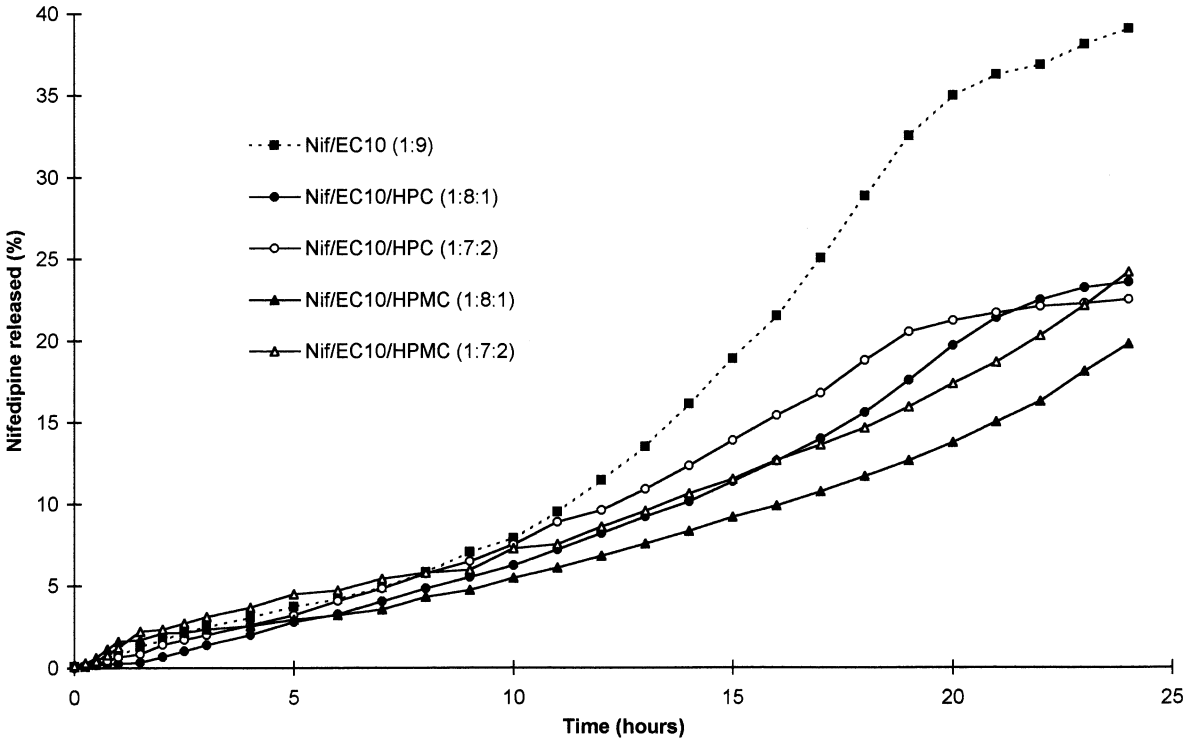


Fig. 6. In vitro release of nifedipine from EC/HPC and EC/HPMC microspheres. Key: see Fig. 1.

cellulose microspheres. The increased drug release when methylcellulose amount was increased in the microspheres formulation was attributed to the presence of more channels being available for diffusion. As in the EC microspheres, the dissolution patterns cannot be simulated by any specific kinetic model properly, and combined kinetics appeared to be more appropriate. Thus, for the first time (0–10 h), kinetic of release was of zero-order from Nif/EC/HPMC microspheres. Between 10 and 24 h the data fit first-order kinetic with coefficient of correlation close to one. Whereas data from Nif/EC/HPC did not fit any specific kinetic model.

## 4. Conclusion

The influence of EC viscosity, drug/polymer ratio and EC/water-soluble polymer ratio on the physical characteristics of microspheres (size, drug loading and kinetic of release) was investigated. From X-ray and DSC results it appeared that experimental conditions used in this work allowed the formation of microspheres having a matrix structure in which nifedipine was uniformly dispersed in molecular state. In vitro release of nifedipine from all prepared microspheres was more regular than that of pure drug. However, in spite of the presence of nifedipine in amorphous state in the microspheres, the rate of the drug release remains low so that such systems do not appear to be appropriate for oral controlled delivery of poorly water soluble drugs.

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