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Microencapsulation of nitrofurantoin in poly(ϵ-caprolactone): tableting and in vitro release studies

C. Dubernet [1], J.P. Benoit [1], G. Couarraze [2] and D. Duchêne [1]

[1] *Laboratoire de Pharmacie Galénique et Biopharmacie, U.A. C.N.R.S. 1218 and* [2] *Laboratoire de Physique, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, Chatenay-Malabry (France)*

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Summary

Nitrofurantoin, an antibacterial agent, has been incorporated into poly(ϵ-caprolactone) microspheres using the solvent evaporation process. Microscopy studies showed that increasing the drug content in the microspheres produced rod-like crystals at the microparticle surface. For all the drug contents investigated, nitrofurantoin formed crystalline domains dispersed in the polymer matrix. When the microspheres were tableted, the cohesion of the compact augmented with increasing the nitrofurantoin content and/or with reducing the mean microsphere diameter. The in vitro release rate of nitrofurantoin from the microspheres could be modified according to the size distribution and the drug loading of the microparticles. Tableting them produced a much slower release rate. Based on the non-linear search procedure, most of the microsphere samples studied exhibited a release profile obeying the Higuchi equation. However, in some cases where the payload was equal to or above 20% (w/w), the early and the middle stage of release followed a first-order kinetic pattern. This deviation from the Higuchi model was believed to be due to the heterogeneity of individuals forming the samples analyzed.

Introduction

Nitrofurantoin, a drug used for the prevention and treatment of urinary tract infections, belongs to the group of drugs that exhibit bioavailability problems (Mendes et al., 1978a and b). In addition, this drug is associated with a number of side-effects, including nausea, vomiting and diarrhoea. A promising way of optimizing its action and reducing its side-effects is to incorporate nitrofurantoin in a sustained release dosage form (Conte et al., 1979; Eldem and Capan, 1983). Since the drug is poorly water-soluble (Martindale, 1982), much care must be taken in the choice of the matrix polymer to obtain a desirable release profile. Poly(ϵ-caprolactone) seems to be a good candidate. This polyester was found to come close to meeting the requirements of a biodegradable reservoir or monolithic device for controlled drug delivery, especially in the contraceptive field (Pitt et al., 1979). The present work was carried out to study the properties of individualized and tableted nitrofurantoin-loaded poly(ϵ-caprolactone) microspheres and to compare their release profiles.

Correspondence: J.P. Benoit, Laboratoire de Pharmacie Galénique et Biopharmacie, U.A. C.N.R.S. 1218, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, 5 rue Jean-Baptiste Clément, 92 296 Chatenay-Malabry Cedex, France.

Materials and Methods

Materials

Poly(ϵ-caprolactone) (Tone P700) was supplied by Union Carbide (New York, NJ, U.S.A.). Its molecular weight was about 40,000 (GPC). Nitrofurantoin was provided by Sigma (Saint Louis, MO, U.S.A.). Its mean diameter as measured with the Coulter counter was 17 μm. Methylcellulose was used as the emulsifying agent (Metolose SM 400, Seppic, Paris, France). A 400 mPa · s grade was chosen. Chloroform was used without further purification (Rectapur, Prolabo, Paris, France).

Methods

Preparation of the microspheres. 80 g poly(ϵ-caprolactone) were dissolved into 400 ml chloroform. A weighed quantity of nitrofurantoin varying from 8.9 to 80 g was then suspended in the organic phase. This suspension was emulsified in a 0.25% (w/w) methylcellulose aqueous solution previously saturated with the drug. The whole system was shielded from light. Three types of agitation of the resulting emulsion were tested:
(a) with a one-bladed stirrer at 700 rpm, until complete solvent evaporation;
(b) with a Microvortex high shear mixer at 3700 rpm for 10 min, 30 min or 5 h. The agitation was then maintained until total evaporation with the first type of stirring;
(c) with an Ultraturax closed-turbine at 1500 rpm for 5 min. The solvent evaporation was led to completion as before. The microspheres were isolated, washed several times with deionized water and methanol, filtered and dried under vacuum.

Size distribution analysis. This was performed by mechanical sieving (Rotolab, Prolabo, Paris, France). For this purpose, 125, 200, 315, 400, 630 and 700 μm sieves were used.

Scanning electron microscopy study. The microspheres were coated with gold and examined under a scanning electron microscope, Cameca (Cameca, Courbevoie, France) equipped with a Polaroid.

Determination of the nitrofurantoin content. A weighed quantity of microspheres (20 mg) was suspended in 16 ml dimethylformamide. After filtration, the volume of the resulting solution was adjusted to 100 ml with deionized water. The solution was spectrophotometrically assayed at 295 nm (Model 25, Beckman, Gagny, France).

Preparation of the mixtures of drug-free microspheres and nitrofurantoin. For this study, only 3 micromeritic fractions of microspheres were used: < 200 μm, 200–400 μm, > 400 μm. Each of these fractions was mixed with 10 or 20% (w/w) nitrofurantoin using a Turbula mixer (Basel, Switzerland), at 32 rpm, for 30 min, in a 100 ml flask.

Thermal and X-ray analyses. Thermal analysis was carried out using a differential scanning calorimeter (Model 990, Du Pont de Nemours, Wilmington, DE, U.S.A.) with samples weighing about 5 mg and contained in aluminum pans. Programmed heating of the samples at a rate of 2°C/min was carried out from 0 to 280°C. X-Ray powder diagrams were obtained with a Rigaku diffraction unit (Rigaku, Tokyo, Japan).

Porosity determination. Measurements were made on a weighed quantity of microspheres (2 g), degassed at room temperature for 1 h. Pore volume was determined by measurement of the mercury volume penetrating the pores or voids within microspheres, using a high pressure Porosimeter, Model 2000, Carlo Erba Instruments (Milan, Italy). Pressure was increased incrementally from atmospheric pressure up to 19×10^7 Pa.

Tableting experiments. These studies were carried out with two different single punch tablet machines: a Korsch (Berlin, F.R.G.) and a Frogerais A0 machine (Vitry s/Seine, France). The Korsch tablet machine was fitted with a 12 mm die and flat-faced punches. A strain-gauge-equipped upper punch was used to measure compression forces ranging from 0 to 3000 daN (TS 26 b Model, Sedeme, Paris, France). The signal after calibration and amplification was recorded on a UV detector (Southern Instruments, Sedeme, Paris, France). For all the formulations, the tablet weight was fixed at 500 mg. The Frogerais tablet machine was equipped with strain gauges on the upper and lower punches. The signals were monitored after calibration and amplification (TS 26 Model, Sedeme, Paris, France) throughout the compression cycle with a computer (Bascom Turner BS 8000, Thorn EMI Technology Montreuil, France). Thus, the

compression forces were recorded versus time. Then, using the computer the lower punch force was plotted against the upper punch force. The tablet weight was fixed at 390 mg. All the experiments were made without any lubrication.

In vitro release experiments. 500 mg of microspheres or a tablet fabricated on the Korsch machine were introduced in a round-bottomed flask (Dissolutest, Prolabo, Paris, France), containing 1000 ml of a phosphate buffer (pH 7.2, 37°C). The medium was agitated at 60 rpm and continuously assayed at 295 nm.

Results and Discussion

Poly(ϵ-caprolactone) was supplied as rods which were impossible to compress. Because of the rubbery state of the amorphous regions, the polymer could not be ground into fine powder before direct tableting. The only method leading to the formation of small and individualized particles was to prepare polymer microspheres by evaporation of a volatile organic solvent from an oil-in-water emulsion (Benita et al., 1984). The so-called solvent evaporation process was appropriate to encapsulate nitrofurantoin after saturation of the aqueous phase with the drug to avoid any partitioning between the two phases.

Size distribution analysis

The size distribution of the drug-free microspheres was influenced by the stirring rate and the shearing nature of the emulsion. Fig. 1 shows the particle size distribution when agitating at 700 rpm with a one-bladed stirrer. The size range went from 45 to 685 μm with a peak between 400 and 630 μm. Increasing the stirring rate at 3700 rpm with a Microvortex propeller, for 10 min, 30 min and 5 h, following the beginning of the solvent evaporation, reduced the width of the size distribution since all the particles had a diameter less than 315 μm. Time during which an important shearing was maintained, did not significantly affect the size distribution which remained centered at 50 μm. The size of microspheres was conditioned by the size of the oil droplets as soon as the oil-in-water emulsion was formed. Replacing the

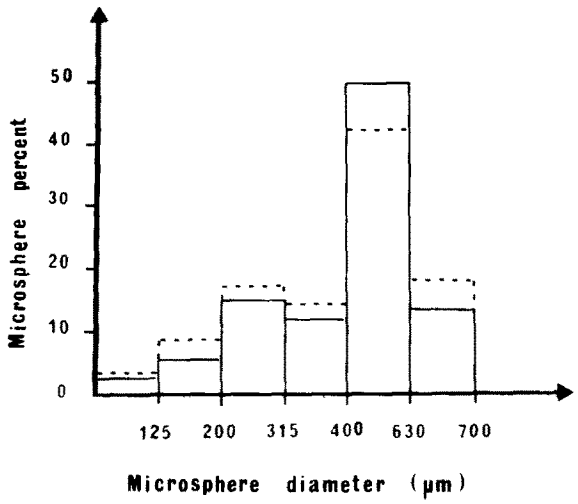

Fig. 1. Size distribution of poly(ϵ-caprolactone) microspheres prepared at 700 rpm with a one-bladed stirrer: ———, non-loaded; - - - - - -, 20% nitrofurantoin-loaded.

Microvortex propeller by an Ultraturax turbine for 5 min at 1500 rpm led to the narrowest size distribution and to a mean microsphere diameter of 30 μm (SEM). This showed that the shearing of the starting emulsion was a factor as important as the stirring rate to control the size of the microspheres. However, its nature remained to be defined. Incorporation of nitrofurantoin (20% w/w) into the microspheres did not significantly affect the micromeritic distribution at 700 rpm (Fig. 1), although an increase in viscosity of the poly (ϵ-caprolactone)/$CHCl_3$ solution was qualitatively observed after adding the nitrofurantoin. It should be emphasized that yields of isolated microspheres were related to final particle size. For microsphere batches composed of large particles, prepared at 700 rpm, the yield was extremely good, superior to 95% recovery. Yields of smaller microspheres prepared with the Microvortex and the Ultraturax propeller were reduced respectively at 85 and 78% recovery. This was due to microsphere losses during successive decantation washings.

Microscopic characterization of the microspheres formed

Poly(ϵ-caprolactone) microspheres prepared using the solvent evaporation process were spherical, individualized but had different surfaces

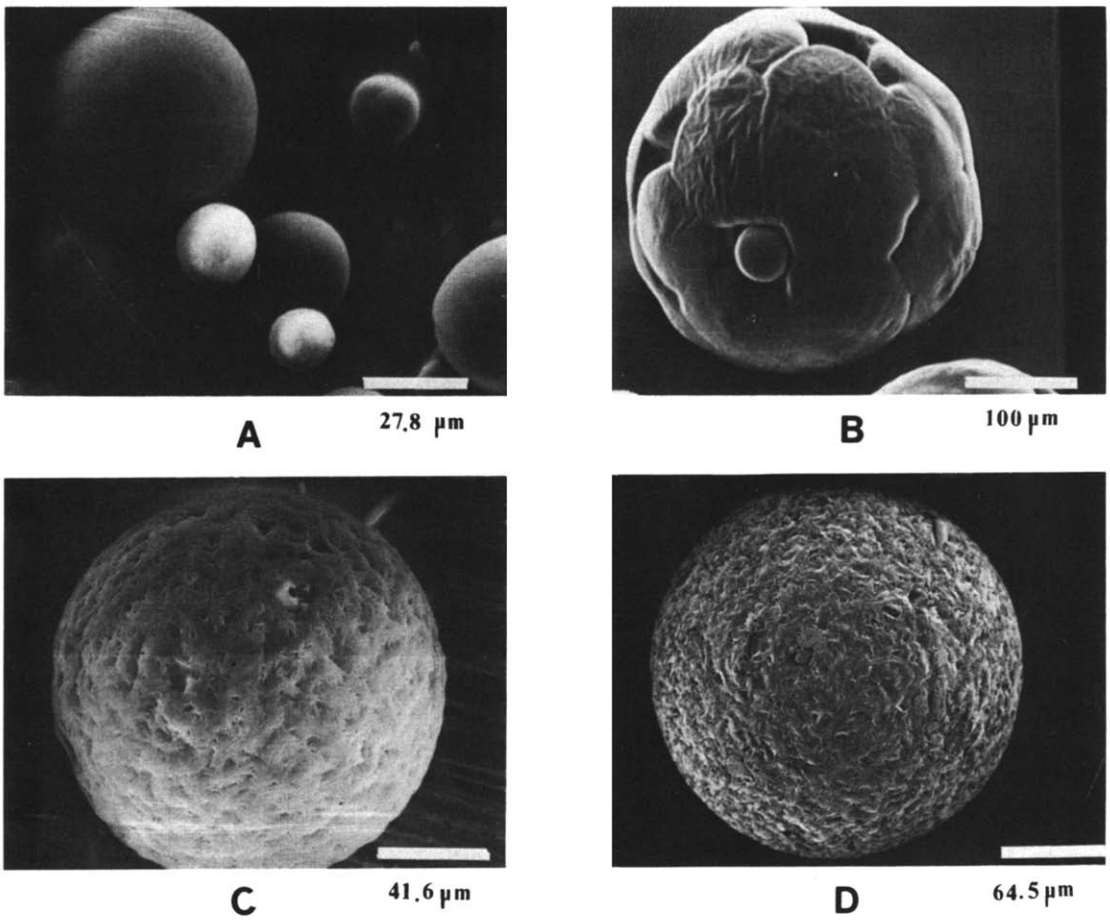

Fig. 2. Scanning electron photomicrographs of poly(ϵ-caprolactone) microspheres. A: non-loaded (×720). B: non-loaded (×200). C: 10% nitrofurantoin-loaded (×480). D: 20% nitrofurantoin-loaded (×300).

according to the initial active ingredient/polymer ratio and their size (Fig. 2). Below 400 µm, the drug-free microspheres exhibited a very smooth surface (Fig. 2A). For a larger diameter, deep cracks were present (Fig. 2B). When nitrofurantoin was incorporated within the polymer matrix, the surface became extremely porous (Fig. 2C). Drug crystals appeared progressively embedded in the surface as soon as the nitrofurantoin content increased from 10 to 20% w/w irrespective of the size (Fig. 2D). At 50% w/w, the particles seemed to be totally coated by the crystals. The same morphological feature was observed when the microsphere size diminished for a drug content of 20%. This point should be taken into account with a view to a drug kinetic evaluation, because of the probable presence of a burst effect in the release profile of nitrofurantoin.

Determination of the nitrofurantoin content in the microspheres

In an attempt to increase the nitrofurantoin content of the microspheres, a number of experiments were performed in which the initial nitrofurantoin/polymer ratio was gradually increased from 10 to 50% (w/w). The data in Table 1 indicate that the incorporation efficiency is always very high since it ranges from 85.5 to almost 100%. The recorded variations between the different microsphere batches were believed to be due

TABLE 1

Effect of initial nitrofurantoin / poly(ϵ-caprolactone) ratio and size range on microsphere drug content and incorporation efficiency

Initial NF/PC ratio (w/w)	Theoretical drug content (%) (w/w)	Size range (μm)	Actual drug content [a] (%) (w/w)	Incorporation efficiency (%)
0.11	10	< 200	8.5	85.5
0.11	10	200–400	9.6	96.6
0.11	10	> 400	9.9	98.9
0.25	20	< 200	18.2	91.2
0.25	20	200–400	18.5	92.7
0.25	20	> 400	18.4	92.1
1	50	< 200	48.5	97.0
1	50	200–400	49.6	99.2
1	50	> 400	49.8	99.6

NF = nitrofurantoin; PC = poly(ϵ-caprolactone).
[a] Mean of 3 determinations.

to the uncontrolled removal of nitrofurantoin during the washing steps. Such high drug payloads were obtained because of the previous saturation of the aqueous dispersing phase with nitrofurantoin. This prevented the drug from partitioning in the water phase.

Determination of the internal structure of the microspheres

The microspheres were prepared under experimental conditions where the polymer and the drug were intimately mixed. Consequently, a large variety of solid dispersions could occur within the particles (Benoit et al., 1986). In an attempt to define the internal structure of the matrix, thermal and X-ray analyses were carried out. A DTA scan of 10% nitrofurantoin-loaded microspheres had two well-defined thermal events: the first one at 60°C corresponded to the fusion of the poly(ϵ-caprolactone) crystalline domains. The second one at 270°C was related to the decomposition of the active ingredient before its fusion (Fig. 3). It should be pointed out that the DTA scan started at −65°C which was the expected glass transition temperature (T_g) of poly(ϵ-caprolactone). Therefore, no information about the influence of the

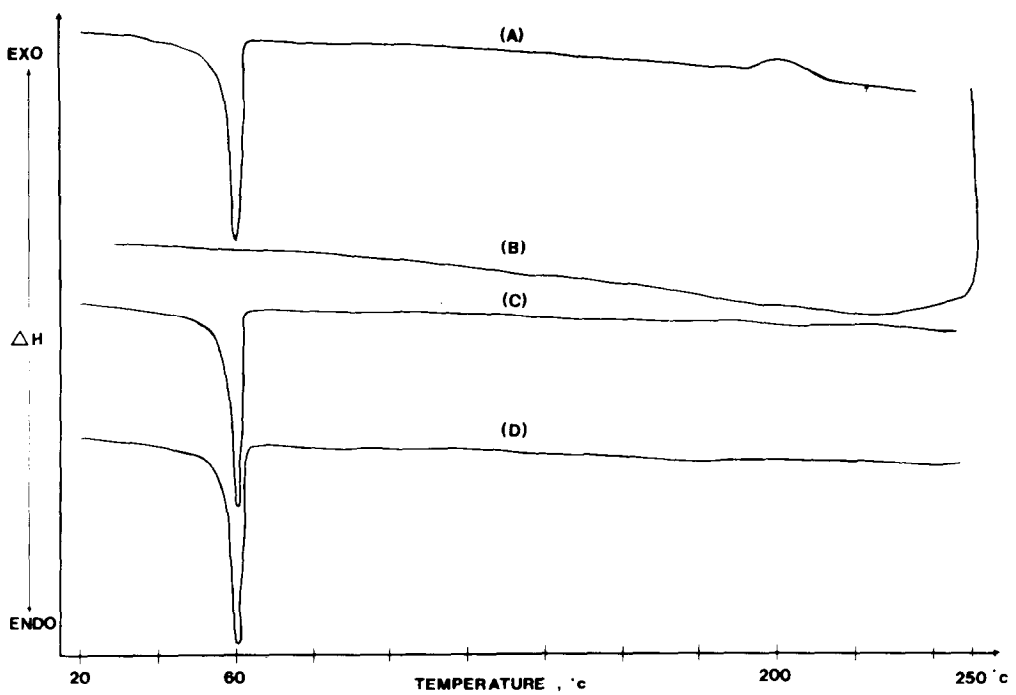

Fig. 3. DTA scans of (A) poly(ϵ-caprolactone), (B) nitrofurantoin, (C) a mixture a poly(ϵ-caprolactone) and nitrofurantoin, and (D) 10% nitrofurantoin-loaded microspheres.

nitrofurantoin on the T_g of the polymer could be obtained. The X-ray powder diagrams of 10 and 20% drug-loaded microspheres had d-spacings characteristic of starting poly(ϵ-caprolactone) and crystalline nitrofurantoin. In view of these results, it was, however, impossible to conclude whether or not all the encapsulated nitrofurantoin is in a crystalline form within the polymer matrix. The only point which would enable the definite establishment of the physical state of the drug, would be the comparison of the fusion heats of nitrofurantoin, alone and encapsulated. Unfortunately, as previously mentioned, nitrofurantoin degraded before melting. However, since the active ingredient was not soluble in the casting solvent used during the evaporation process, it was more likely that the drug formed only crystalline domains within the microspheres. Fig. 3 shows also that the microencapsulation of nitrofurantoin in the poly(ϵ-caprolactone) did not improve the thermal stability of the drug. On the other hand, the presence of nitrofurantoin, encapsulated or not, protected the polymer against a thermal decomposition starting at 200–210°C. If solid solution-type interactions did not exist between the drug and the polymer in the microspheres, it appeared that a number of interactions developed when the poly(ϵ-caprolactone) melted. Their nature remains to be defined.

Study of the compression of the microspheres

In the present study, the nitrofurantoin-loaded microspheres (10 and 20%) were compared with physical mixtures of drug-free microspheres and nitrofurantoin at the same ratio. Both formulations had a remarkable flowability. In the case of

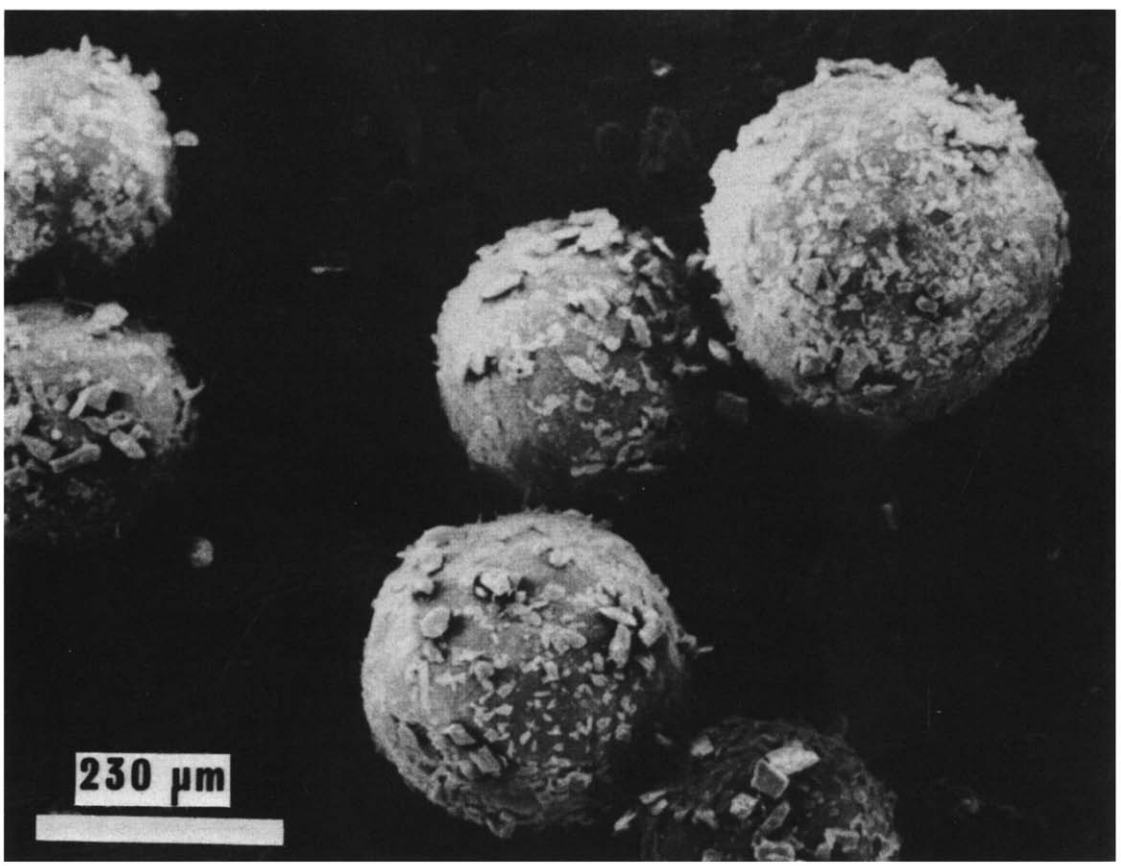

Fig. 4. Scanning electron photomicrograph of a physical mixture of drug-free microspheres and nitrofurantoin at 10% w/w (×100).

TABLE 2

Effect of the presence of nitrofurantoin, encapsulated or not, on tablet characteristics (hardness and force recorded on the upper punch)

Size range:	< 200 μm			200–400 μm			> 400 μm		
Compression volume (mm^3):	309	316	337	309	316	337	309	316	337
Non-loaded microspheres									
Hardness (N)	0	0	0	0	0	0	0	0	0
Force (daN)	1215	2130	2670	> 3000	> 3000	> 3000	> 3000	> 3000	> 3000
10% NF-loaded microspheres									
Hardness (N)	19.62	20.60	22.56	0 [a]	0 [a]	0 [a]	0	0	0
Force (daN)	900	1710	1770	> 3000	> 3000	> 3000	> 3000	> 3000	> 3000
20% NF loaded microspheres									
Hardness (N)	26.49	33.35	41.20	26.49	29.43	29.43	9.81	9.81	19.62
Force (daN)	555	900	1395	2355	> 3000	> 3000	> 3000	> 3000	> 3000
10% NF mixture [b]									
Hardness (N)	0	0	0	0	0	0	0	0	0
Force (daN)	945	1800	1980	1365	2310	2460	> 3000	> 3000	> 3000
20% NF mixture [b]									
Hardness (N)	0	0	0	0	0	0	0	0	0
Force (daN)	360	690	1485	480	915	990	> 3000	> 3000	> 3000

[a] Slightly cohesive after tableting.
[b] Mixtures performed for 30 min.

the physical mixtures, scanning electron microscopy showed that all the drug particles were fixed by adhesive forces on the surface of the microspheres (Fig. 4). This could explain the good free-flowing properties of such formulations. Two parameters characteristic of the compact obtained were measured: hardness and the upper punch force developed. The results are recorded in Table 2. The cohesion of the tableted drug-loaded microspheres increased with increasing drug content, for a given pressure. In contrast, it diminished with an increase in the mean microsphere diameter. Concerning the unloaded and the 10% nitrofurantoin-loaded microspheres (200–400 μm fraction), although the recorded hardness was zero in both cases, only the compacts obtained from the drug-loaded microspheres remained cohesive after compression. It was concluded that the presence of nitrofurantoin crystals firmly attached to the microsphere surface favored strong interparticle bondings in the compression process. It was interesting to note that, in the same experimental conditions, hardness of the tablets fabricated from the physical mixtures of drug-free microspheres and nitrofurantoin was zero, irrespective of the size particle distribution studied. It was believed that elastic recovery of poly(ϵ-caprolactone) after compression was responsible for the absence of cohesion between its particles inside the compacts, and also made anchoring of the nitrofurantoin particles at their surface impossible. The comparison of the forces recorded on the upper punch enabled one to assess the degree of resistance of the different materials to their compression, for a given mass. The recorded forces diminished with reducing microsphere size, whether the nitrofurantoin was encapsulated or not. The effect of particle size on the cohesion of the tablets was expected since it was known that fine-grained powders gave tablets of a higher strength than coarse-grained ones, on account of the greater area of interparticle contact (Hüttenrauch, 1977). Furthermore, the rearrangement of fine powders is greater than that of coarse ones: this explains the decrease of the forces recorded on the upper punch with microsphere size. For the 200–400 μm fraction, based on the developed forces, the rearrangement of nitrofurantoin-loaded microspheres inside the

compact was probably very limited. This could be opposed to the behavior of the physical mixtures during compression, owing to the presence of nitrofurantoin in the external phase. In addition, these results proved, indirectly, that no bonding by melting of the microspheres occurred during compression in spite of the low fusion temperature of poly(ϵ-caprolactone) (60°C). This last point was confirmed by microscopic observations of the tableted spheres.

The charts of the lower punch force/upper punch force cycles, carried out with a Frogerais tableting machine, enabled the establishment of the relationship between the area enclosed in the resulting hysteresis loop, A, and the maximal recorded upper punch force, F. According to Fessi et al. (1981), a plot of A versus F was parabolic for substances which underwent a fragmentation under compression.

$$A = aF^2 + bF + c \quad (1)$$

therefore for high values of F:

$$\log A = 2 \log F + \log a \quad (2)$$

Fig. 5 shows the plots obtained with nitrofurantoin alone and with drug-free poly(ϵ-caprolactone)

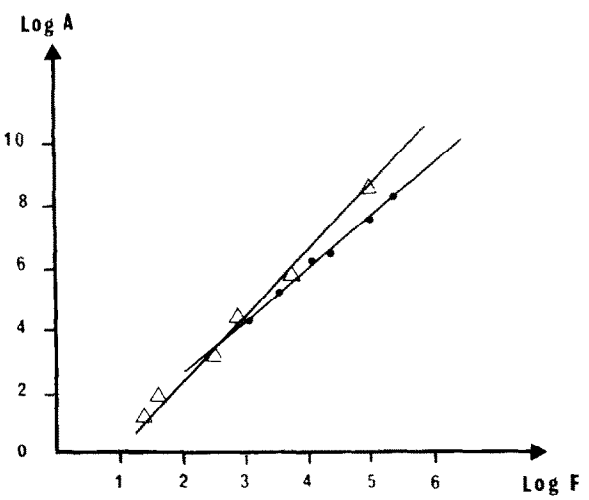

Fig. 5. Relationship between the area of the hysteresis of the lower punch force/upper punch force cycle, A, and the maximal recorded upper punch force, F.

microspheres. Both materials exhibited a linear relationship on a log–log representation. As expected, Eqn. 2 was verified for nitrofurantoin with a slope of 2.15. This confirmed the behavior of the drug which underwent brittle fracture during compression (Ponchel et al., 1986). But it was surprising to observe such a linearity with poly(ϵ-caprolactone) microspheres since their deformation did not occur via fragmentation but rather via plastic flow under pressure. The only explanation of the inconsistency between the behavior of the poly(ϵ-caprolactone) microspheres during compression and the viscoelastic properties of the polymer, could be that Carstensen's theory was appropriate to characterize substances with no porosity such as a macrocrystal, but not to microspheres which constitute a porous system: 40–50 $mm^3 \cdot g^{-1}$ for drug-free poly(ϵ-caprolactone) microspheres as measured by the mercury intrusion method.

Finally, it should be noted that the microspheres did not rupture under compression.

In vitro drug release

In vitro nitrofurantoin release experiments were performed with individualized and tableted microspheres. In the case of well-defined microspheres, the effects of their size distribution and their drug loading on the drug release profiles were determined (Figs. 6 and 7). As expected, decreasing the size distribution increased the release rate of nitrofurantoin due to an enhancement of the specific area of the microparticles (Fig. 6). Fig. 7 shows that increasing the drug content in the microspheres enabled one to increase significantly its release rate. Tableting the microspheres produced a much slower release rate which could be decreased by increasing tablet hardness (Fig. 8). This probably reflected a decrease in the porosity of such systems during compression. In addition, experimental observations showed that nitrofurantoin dissolution took place mainly on the surface of the compact.

Nitrofurantoin-loaded microspheres (20%) were isolated from the middle of tablets made at 1500 daN after being immersed 56 h in the release medium, and examined by SEM. They were not attacked by the extraction solvent. This showed that solvent penetration inside the compact was

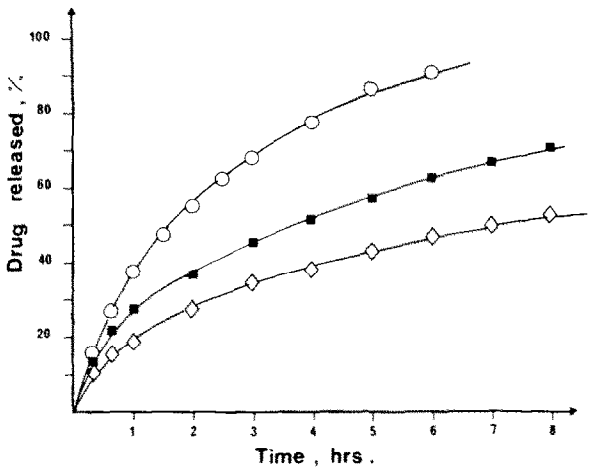

Fig. 6. Effect of size distribution on nitrofurantoin release from 20% loaded microspheres: ○, < 200 μm; ■, 200–400 μm; ◇, > 400 μm.

greatly slowed down because of its low porosity.

A kinetic analysis was carried out for non-tableted microspheres in an attempt to determine the phenomena that govern the release pattern of nitrofurantoin from poly(ϵ-caprolactone) microspheres. It is generally accepted that the first-order equation and the Higuchi square-root of time equation can best be used to describe the overall release pattern of a drug from microspheres (Benoit et al., 1984). Accordingly, the applicability of

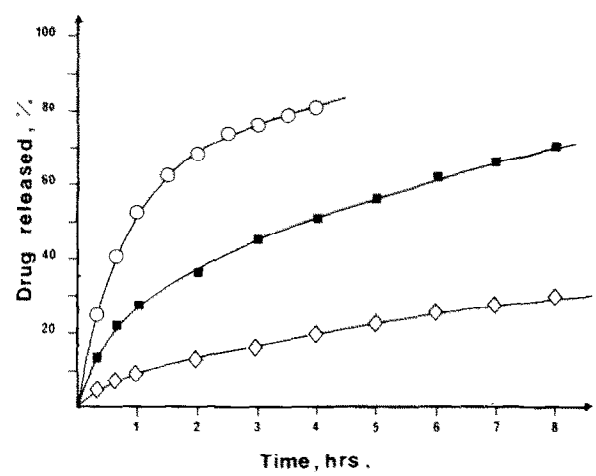

Fig. 7. Effect of drug loading on nitrofurantoin release from 200–400 μm microspheres: ◇, 10%; ■, 20%; ○, 50%.

the classical first-order equation was examined according to the following expression:

$$Q = W_0(1 - e^{-kt}) \tag{3}$$

where W_0 is the initial quantity of drug in the microspheres and k is the first-order release constant. In the same way, Higuchi's law was taken into account according to its simplified form:

$$Q = kt^{1/2} \tag{4}$$

where k is the release rate constant. For the purpose of identifying the correct overall release kinetic model, the non-linear least-squares regression search procedure was used (Bevington, 1969). It is considered the most appropriate mathematical and statistical treatment available to distinguish between the various kinetic models in the present study. This statistical method, using the kinetic experimental results without any further transformation, was applied to identify the drug release mechanism either from microcapsules (Benita and Donbrow, 1982) or from microspheres (Benoit et al., 1984). This search leads to the best-fit curve expressed by the appropriate minimum value of χ^2 for each of the two expected kinetic models (Eqns. 3 and 4), taking into consideration the experimental data obtained. Table 3 reports all the χ^2 values yielded by the two kinetic equations when they were applied to the overall release of nitrofurantoin from microsphere batches having different size distribution and different drug contents (10–50%).

The fitness of the experimental data to the theoretical kinetic laws was obtained for a χ^2 less than 10 (Hoffman et al., 1986). Thus, it can be seen from Table 3 that most of the microsphere samples studied presented a release profile obeying the square-root of time equation. Only the 20% drug-loaded microspheres with diameters smaller than 200 μm and the 50% ones with diameters smaller than 400 μm did not exhibit such a release pattern ($\chi^2 \geqslant 13.06$). To gain more insight in this unexpected behavior, the non-linear search analyses were performed on different portions of all the release curves: 0–20%, 20–40% and 40–60% (Table 4, Figs. 9 and 10). The late release

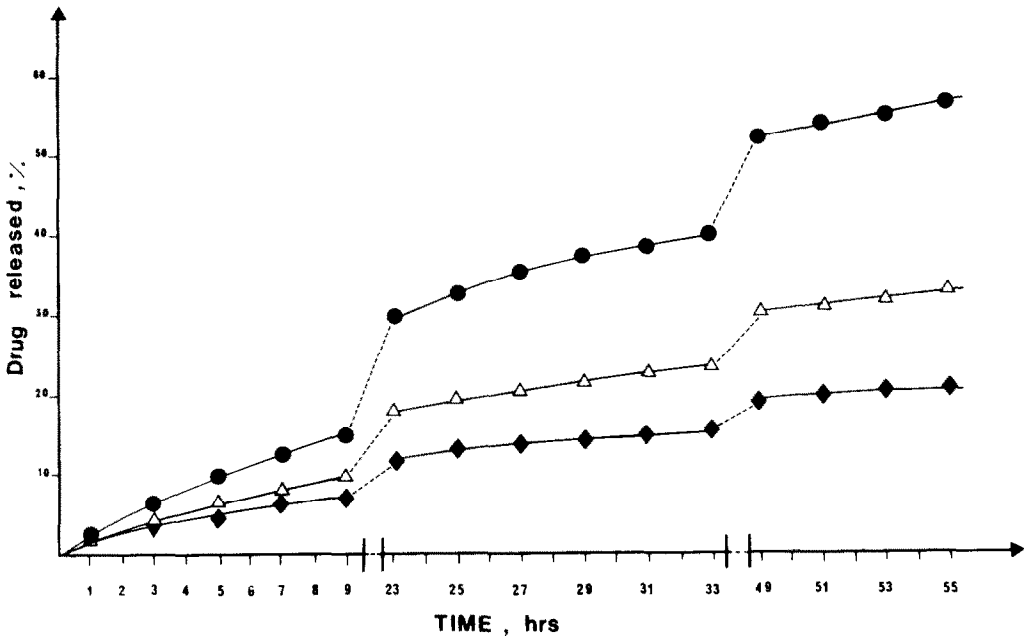

Fig. 8. Effect of tablet hardness on nitrofurantoin release from tableted microspheres: ◆, 107.9 N (50% drug loading); △, 49.0 N (20% drug loading); ●, 9.8 N (10% drug loading).

of nitrofurantoin, above 60%, was not taken into consideration, (Higuchi, 1963). Based on the χ^2 values, Table 4 shows that the deviation to Higuchi's law is mainly observed in the early stage (0–20%) of the release for the 20% drug-loaded

TABLE 3

χ^2 values obtained after comparison of the simulated release curves from Higuchi's law and the first-order law, to the observed kinetic data

Theoretical drug content (%) (w/w)	Size range (μm)	Drug released (%)	χ^2	
			Higuchi's law	First-order law
10	< 200	73.6	2.25	26.75
	200–400	35.1	1.06	9.19
	> 400	33.1	1.31	10.76
20	< 200	90.2	13.06	6.12
	200–400	76.3	2.35	47.20
	> 400	88.5	7.53	51.37
50	< 200	98.6	out of range	4.67
	200–400	81	28.25	29.03
	> 400	61.4	5.68	28.00

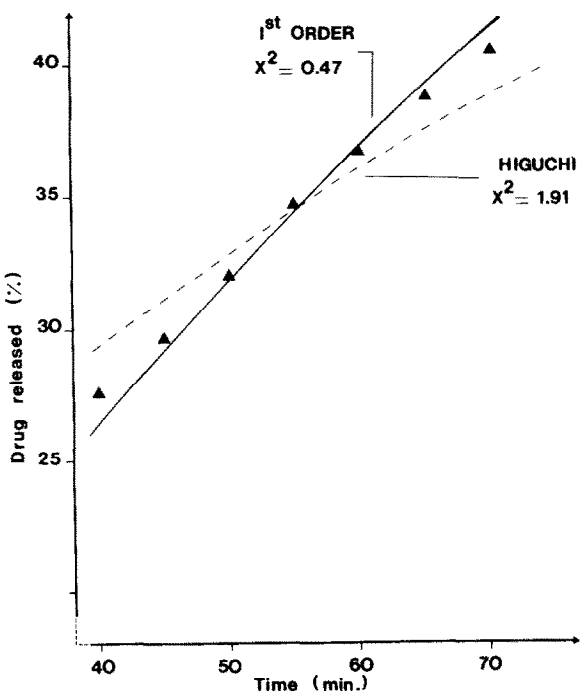

Fig. 9. Fitting and comparison of the predicted release curves as determined by the computer according to the square-root of time equation (- - - - - -) and first-order equation (———) to observed kinetic data (▲); 20% nitrofurantoin loading, < 200 μm fraction.

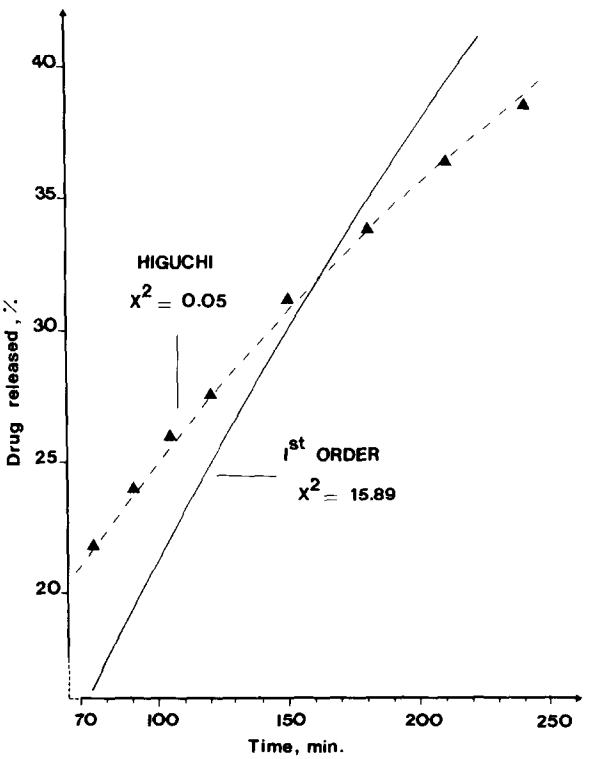

Fig. 10. Fitting and comparison of the predicted release curves as determined by the computer according to the square-root of time equation (- - - - - -) and first-order equation (———) to observed kinetic data (▲); 20% nitrofurantoin loading, > 400 μm fraction.

microspheres with diameters smaller than 400 μm and the 50% ones, irrespective of the size. This deviation is also noted in the middle stage (20–40%) of the release of nitrofurantoin from the smallest size distribution fractions (20 and 50% payload). Although a burst effect was not clearly displayed for the 20% and 50% loaded samples (Figs. 6 and 7), the inability to fit the results to the Higuchi law in these cases was believed to be due to the drug crystals embedded in the microparticle surface. This morphological characteristic, probably different from one particle to another, might indicate the high heterogeneity of the studied ensembles. By analogy to recent work dealing with the release of different active ingredients from microcapsules (Hoffman et al., 1986; Gross et al., 1986), this last point might explain the attainment of a first-order law describing the experimental data instead of the expected Higuchi's law. Nevertheless, despite some deviations, it seems that the release of nitrofurantoin from poly(ϵ-caprolactone) microspheres is governed by a non-erodible matrix release mechanism (Higuchi, 1963).

The results reported here indicate that an antibacterial such as nitrofurantoin can be encapsulated in poly(ϵ-caprolactone). The release profiles of these microspheres can be modified: (a) by changing their particle size; (b) by controlling the

TABLE 4

χ^2 values obtained after comparison of the simulated release curves, from Higuchi's law and the first-order law, to the observed kinetic data for the early release of nitrofurantoin

Theoretical drug content (%) (w/w)	Size range (μm)	0–20% release χ^2		20–40% release χ^2		40–60% release χ^2	
		Higuchi's law	First-order law	Higuchi's law	First-order law	Higuchi's law	First-order law
10	< 200	2.26	2.16	0.30	7.86	0.12	5.16
	200–400 [a]	0.27	6.13	–	–	–	–
	> 400 [a]	0.23	3.57	–	–	–	–
20	< 200	5.98	0.29	1.91	0.47	0.51	1.10
	200–400	2.14	1.35	0.17	11.46	0.48	11.89
	> 400	0.32	4.79	0.05	15.89	0.70	9.22
50	< 200 [b]	–	–	–	–	–	–
	200–400	10.99	0.94	3.69	0.27	0.44	2.15
	> 400	5.01	0.25	1.09	3.58	2.53	20.87

[a] The experiment was stopped when 35% and 33% of drug was released.

[b] Release was too fast to enable the analysis of the initial portions of the release profile.

drug loading; and (c) by tableting the microspheres. Compression considerably slows down the release of nitrofurantoin, since the compact obtained is relatively impermeable to the solvent. The use of a suitable disintegrant would solve this problem and lead to the combination of the advantages of the tablet form and those of a microparticle matrix system.

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