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Mechanism of drug release from silicone microspheres containing Polycarbophil

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Abstract

The possibility of a pH-controlled drug release mechanism applying to silicone microspheres containing nicotinamide (NAM) and Polycarbophil (PCP), a pH-sensitive hydrogel, is evaluated. NAM-medicated PCP in the 4:1 PCP-NAM wt ratio is dispersed, at the 20% or 40% concentration, in silicone in the form of osmotically active particles of around 15 μm mean volume diameter, and encapsulated in microspheres in the 105–710 μm size range by a modified emulsion vulcanization technique, with a 100% entrapment efficiency. The external and internal morphology of microspheres, and the size distribution of PCP-NAM particles dispersed therein are evaluated by scanning electron micrography. Microspheres are eluted 9 h with simulated GI fluids (pH 1.2–7.4). Assessment of the time exponent characterizing the release kinetics, together with release and swelling data from planar matrices of same formulation as the microspheres, substantiate the following release mechanism. Due to their small size, the osmotically active particles have a limited ability to crack the silicone polymer and interconnect upon swelling, so the hydrogel route of release is of a minor relevance, and so is the hydrogel pH-sensitivity. Drug release is mainly governed by partitioning-diffusion in the silicone continuum of microspheres, therefore it is pH-independent and the time exponent is close to the value typical of Fickian release. It is concluded that encapsulation of hydrogel particles of larger size is a necessary condition for a pH-controlled release pattern. © 1997 Elsevier Science B.V.

Keywords: Silicone; Microspheres; Polycarbophil; Nicotinamide; Release mechanism; Oral delivery system

1. Introduction

In previous papers, disk-shaped silicone-based matrices for controlled release of different drugs to the GI tract have been described (Bilia et al., 1996; Buonaguidi et al., 1997). With these systems, drug release is controlled by dispersed granules of pH-sensitive hydrogels, with the following mechanism. The osmotically active hydrogel granules uptake water from the dissolution medium

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and swell. The drug, included in granules, dissolves and diffuses in the swollen granules rather than in the silicone elastomer. In gastric fluid (pH 1–2), the swelling degree is low and the release is essentially controlled by dissolution-diffusion from granules in contact with the matrix surface. In intestinal fluid (pH ~ 7), the hydrogel swelling degree increases, so the number of interconnections and the contact surfaces between adjacent granules tend to increase, thus causing a progressive increase of the apparent diffusivity of drug in matrix. Altogether, the hydrogel responds to the pH changes experienced during matrix transit across the GI tract with a swelling pattern appropriate to provide an extended drug release in the intestinal region and, in some cases, to control the release kinetics to a pseudo-zero order.

It was felt worthwhile to evaluate the possibility of a similar release mechanism applying to a multiparticulate system, consisting of silicone microspheres containing, in dispersion, medicated microparticles of a pH-sensitive hydrogel. Indeed, multiparticulate release systems offer several advantages over single unit systems. Among these, the possibility of combining various types of subunits in a single system, more reproducible transit times across the GI tract, distribution over a vast surface area minimizing the risk of localized damage to the intestinal mucosa. In the present work, Polycarbophil (PCP), a commercial product consisting of crosslinked polyacrylic acid, has been tested as the pH-sensitive hydrogel. According to the manufacturer, PCP absorbs water up to 15–35 ml/g at pH 1–3, or 100 ml/g at neutral pH. Nicotinamide was chosen as a model drug, since it is supposed to dissolve-diffuse in aqueous pores rather than in silicone, due to its high water solubility (0.67 g/ml, according to Remington, 1995). A further aim of the present work has been to contribute to the methodology of preparation of silicone microspheres, since only limited attempts are found in the literature (Chithambara Thanoo and Jayakrishnan, 1991; Lee and Lum, 1992; Maincent et al., 1995; Sutinen et al., 1995).

2. Materials and methods

2.1. Materials

The following commercially available materials were used as received. Nicotinamide (NAM) (Sigma, St. Louis, MO, USA), Polycarbophil (PCP) (Noveon AA1, Goodrich, Cleveland, OH, USA), liquid paraffin (Olio di Vaselina, Carlo Erba, Milan, Italy) and soft paraffin (Vaselina Filante, Carlo Erba, Milan, Italy).

Silbione RTV 70141, composed of part A and part B, was a gift from Rhône-Poulenc Italia S.p.A., Milan, Italy. Silbione RTV 70141 is a two-component viscous-liquid medical-grade polydimethylsiloxane (PDMS) which, upon mixing of the two constituents, is transformed into a rubber by room temperature vulcanization. Higher temperatures reduce the vulcanization time. According to the manufacturer, the crosslinking of the polymer is based on the following reaction:

$$\equiv \mathrm{SiH} + \mathrm{CH_2} = \mathrm{CH} - \mathrm{Si} \equiv \rightarrow$$
$$\equiv \mathrm{Si} - \mathrm{CH_2} - \mathrm{CH_2} - \mathrm{Si} \equiv$$

2.2. Preparation of silicone microspheres and disk matrices

Dispersions (1 g) of 20% or 40% NAM-medicated PCP (4:1, 7:3 or 3:2 PCP-NAM wt ratio) in silicone elastomer were prepared by the following procedure. A solution of a weighed amount of NAM in methanol was equilibrated overnight with a weighed amount of PCP. The methanol-PCP proportion was generally 10 ml/g. The resulting gel was levigated portionwise into a weighed amount of part A of the silicone prepolymer, under a stream of warm air, until complete evaporation of solvent. Since methanol is hardly miscible with silicone and not irreversibly bound to PCP, its removal was considered complete when the mix attained a constant weight. Part B of the prepolymer was admixed, using a spatula, in the proportion of 10 wt% of part A, then the mix was spread as a thin layer on a glass plate and degassed.

To prepare the microspheres, the one-gram mix, immediately after degassing, was poured into a plastic tube equipped with a piston and, thereby, injected into a fluid mass (25 g) of soft paraffin, contained in a beaker of 5 cm diameter, thermostated at 60°C, stirred at 220 r.p.m by a glass propeller of 4.5 cm diameter operated by an overhead stirrer. Dispersion of the silicone mix took place in 20 s, after which the stirring was stopped and the paraffin rapidly thickened by immersing the dispersion in an ice bath, which stabilized the silicone droplets in their dispersed state. The droplets were then allowed to vulcanize by keeping the dispersion 4 days at 37°C, at which temperature the dispersion stayed stable. To recover the microspheres, the dispersion was fluidized, by adding 200 wt% liquid paraffin and heating to 65°C, then filtered through a 105 μm sieve. The material remaining on the sieve was washed at room temperature with liquid paraffin and, next, with petroleum ether to remove the paraffin. The removal was considered complete when the washings, evaporated to dryness, showed no appreciable residuum. The microspheres were then added with excess talc and air dried to a constant weight to ensure a complete removal of petroleum ether. Free-flowing, sievable microspheres were only obtained with the formulations containing the 4:1 PCP-NAM wt ratio.

To prepare the disk matrices, dispersions of 10, 20 or 40% PCP-NAM (4:1 w/w) in the silicone prepolymer were prepared as described above. After degassing, they were thickened by keeping them for 15–20 min at 50°C, then pressed between plastic plates separated by spacers, to form 0.05-cm thick sheets from which, after 24 h vulcanization at 50°C, disks of 0.8 cm diameter were cut. All disks were elastic and their surfaces smooth, non-tacky and hydrophobic.

2.3. Check on silicone vulcanization

This check consisted in determining the wt fraction of material extractable from microspheres or disk matrices, formulated with the 4:1 PCP-NAM wt ratio, by a solvent, such as xylene, able to swell the crosslinked and dissolve the uncrosslinked silicone. Weighed samples were immersed in excess xylene and kept 15 days at room temperature, after which the solvent was filtered off and the samples were dried to constant weight. The extractable fraction was calculated as:

$$\frac{\text{(Initial sample wt)} - \text{(Dry extracted sample wt)}}{\text{(Initial sample wt)} - \text{(PCP-NAM wt in sample)}}$$

The PCP-NAM wt in sample could be calculated, knowing the NAM wt in sample (see next section) and the PCP-NAM wt ratio. The calculated extractable fraction was $7.5 \pm 0.5\%$ ($n = 5$) for the microspheres and $9.5 \pm 0.5\%$ ($n = 5$) for the disks. The vulcanization was therefore considered satisfactory.

2.4. Kinetic measurements

An accurately weighed (10^{-5} g) microsphere sample (15 mg) in the 105–250, 355–425 or 500–710 μm size range was introduced into a screw-capped glass vial. At time zero, a measured volume of dissolution medium (5 or 10 ml, depending on release rate) was added and the vial fixed radially to a wheel mixer rotating vertically at 13 r.p.m. in an atmosphere thermostated at 37°C. At measured time intervals, the stirring was interrupted, the microspheres were allowed to settle, the dissolution medium was withdrawn, using a syringe equipped with a stainless steel needle (25 $G^{5/8}$ 0.5×16 mm), and replaced with the next fraction, then the stirring was resumed. The entire operation took 2–3 min. Each fraction of dissolution medium, after passing through filter paper to remove traces of talc, was analyzed for the drug content. Sink conditions were maintained throughout the release experiment. If not otherwise indicated, samples were eluted with simulated gastrointestinal fluids, consisting of the following solutions: HCl 0.04 M, pH 1.2, made isotonic with NaCl, phosphate buffer pH 6.8, 0.13 M, made isotonic with NaCl, and phosphate buffer pH 7.4, 0.13 M, isotonic. Such solutions were used in sequence, the solution at pH 1.2 and that at pH 6.8 for 2 h each, the solution at pH 7.4 until the end of experiment. Following the release test, the sample was completely depleted of drug by extracting with 5–10 ml of ethanol-water (1:1), in order to determine the initial drug content in

the microspheres, as the sum of released and extracted amounts. One week at room temperature was sufficient for quantitative extraction, as shown by successive determinations.

With the disk matrices, matrix swelling and drug release kinetics were concurrently determined. The experimental apparatus and procedure were those described above for the microspheres, with the following modifications. The withdrawal of every fraction of dissolution medium was carried out simply by pouring. Immediately after every withdrawal, the disk was blotted dry and weighed (swollen weight), then immersed in the next fraction of dissolution medium. The disk was not extracted, after the release test, since quantitative extraction would have required an unreasonably long time, but rather, the theoretical drug load in matrix was taken as the actual value.

The drug was assayed spectrophotometrically, as described in a previous paper (Bilia et al., 1996). Blank runs demonstrated negligible interferences with the measurements.

2.5. Morphology and size distribution of microspheres

The size distribution of microspheres in the 105–710 μm range was determined by sieving. Sieves of 105, 250, 355, 425, 500 and 710 μm mesh sizes were used. The morphology of microspheres and the size distribution of the NAM-medicated PCP particles dispersed in silicone were evaluated by scanning electron micrography (SEM) (Jeol JSM-5200). Samples were mounted on aluminum stubs and sputter coated with gold (10^{-2} bar, 50 s, 20 mA) (Balzers CPS 030). Particle size was measured by image analyis from micrographs of sections of disk matrices. Number and volume size distributions were determined by measuring at least 200 particles per sample.

2.6. Differential scanning calorimetry (DSC) measurements

A Mettler TA 3000 Thermal Analysis System, consisting of a TC-10 TA processor, DSC 20 measuring cell and printer-plotter, was used. Samples of 8–10 mg were scanned in sealed aluminum pans in the 50–200°C temperature interval, at the heating rate of 10 K/min. Samples were obtained by allowing methanolic PCP gels containing NAM, prepared as described before, to evaporate to dryness.

3. Results and discussion

3.1. Preparation of microspheres

In a preliminary approach, the method described by Sutinen et al., 1995 was adopted. Accordingly, the fluid silicone prepolymer was dispersed in liquid paraffin at room temperature, then the temperature was raised to 70°C, under continuous stirring, in order to favour curing of the elastomer. However, the prepolymer droplets were seen to cluster on curing. A similar phenomenon was observed by Chithambara Thanoo and Jayakrishnan, 1991 in a dispersion of silicone prepolymer in aqueous medium. Therefore, soft paraffin was used as the medium, and its property of being fluid above 60°C, semisolid below 37°C, was exploited to stabilize the dispersion, as described in the experimental section of this report.

As stated before, completely vulcanized, free-flowing microspheres were only obtained with the formulations containing the 4:1 PCP-NAM wt ratio, whereas with the 7:3 and 3:2 ratios silicone particles of irregular shape, as observed through a stereomicroscope, and poor flow properties were obtained, due to incomplete vulcanization. Apparently, NAM interfered with the silicone crosslinking reaction and PCP contrasted such an interference, the more so, the higher was its ratio to NAM. Probably, PCP acted by binding NAM via its carboxyl groups. In fact, as shown by DSC measurements, PCP in the 3:2 wt ratio to NAM lowered the heat of fusion of the drug from 189.9 to 69.7 J/g, whereas the fusion peak virtually disappeared with the 4:1 PCP-NAM wt ratio.

Henceforth, only data on microspheres formulated with PCP-NAM (4:1 w/w) will be discussed.

The yield of the preparation method, expressed as wt% of microspheres obtained from the total mass of silicone mix processed, is reported in

Table 1
Yield of preparation and entrapment efficiency for silicone microspheres containing different concentrations of dispersed PCP-NAM (4:1 w/w)

Dispersed phase concentration (%)	Yield (S.D.) % [a, c]	Size range of microspheres (μm)	Entrapment efficiency (S.D.)[b, c]
20	60.2 (7.5)	105–250	0.96 (0.02)
		355–425	0.95 (0.03)
		500–710	0.96 (0.04)
40	59.6 (8.3)	105–250	0.97 (0.03)
		355–425	0.96 (0.02)
		500–710	0.95 (0.04)

[a] Wt% of microspheres recovered, based on the mass of silicone mix processed.
[b] Ratio of experimental to theoretical drug load in microspheres.
[c] Mean and S.D. of three preparations.

Table 1 for microspheres formulated with 20 and 40% dispersed phase. The yield, not significantly different for the two formulations, was substantially lowered by a portion of silicone mix sticking to the centre of the stirring propeller. In Table 1 is also found, for representative size ranges of each microsphere formulation, the entrapment efficiency, expressed as the ratio of experimentally determined to theoretical drug load in microspheres. As it is observed, the entrapment efficiency is always close to unity, thus indicating that the silicone mix remained homogeneous upon dispersion in the fused paraffin. The theoretical drug load was calculated without considering the contribution of the talc adsorbed on the microsphere surface to the microsphere weight. Such a contribution was indeed negligible, as confirmed by the entrapment efficiency values.

3.2. Size distribution of microspheres

Fig. 1 shows the size distribution of microspheres containing 20% or 40% PCP-NAM, as determined by sieving. It is seen that the major contribution to the weight of the microspheres recovered is given by the fraction in the 105–250 μm range, for the former formulation, or that in the 250–355 μm range for the latter. In both cases, around 90% of the microspheres recovered was in the 105–710 μm size range. The prevalence of finer sizes in the formulation containing the lower fraction of dispersed phase may depend on an easier dispersion of this formulation in the fused paraffin, due to a lower bulk viscosity of the silicone mix.

3.3. Morphology of microspheres

The SEM in Fig. 2a evidences the virtually spherical shape of microspheres of comparatively small size. Higher sizes tended to turn oval, as Fig. 2b shows. The rough surface of microspheres is due to adsorbed talc particles. The cross section of a microsphere, seen in Fig. 2b, shows a negligi-

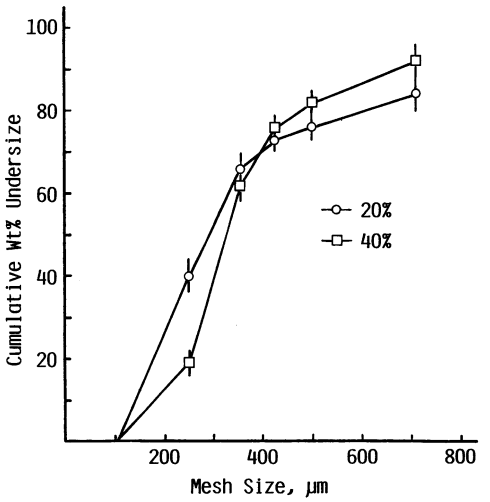

Fig. 1. Size distribution of silicone microspheres containing 20 or 40% dispersed PCP-NAM (4:1 w/w), as determined by sieving. Means and S.D. for three batches.

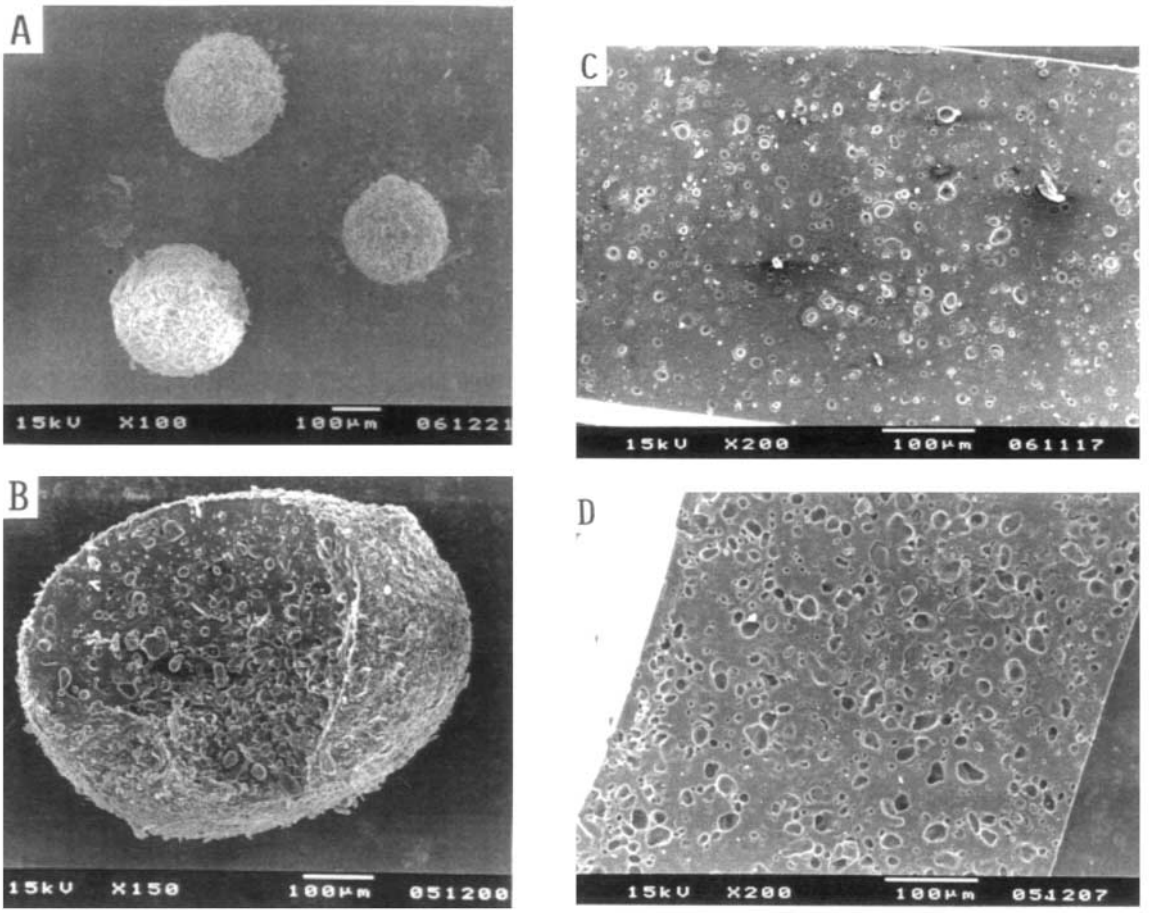

Fig. 2. Scanning electron micrographs showing the external (a) and internal (b) morphology of microspheres, and the distribution of the PCP-NAM (4:1 w/w) particles in silicone at the 20% (c) or 40% (d) concentration.

bly small thickness of the adsorbed talc layer. Fig. 2b also shows a complete encapsulation of the PCP-NAM particles by the silicone elastomer, as well as a random distribution of particles within the whole microsphere volume. The size distribution of the PCP-NAM particles dispersed in silicone was determined by image analysis of SEM of cross sections of disk matrices. Representative micrographs for 20 and 40% dispersed phase are shown in Fig. 2c and 2d, respectively. Particles were classified on the basis of their diameter, as calculated from the projected area. Diameters below 5 μm were not classified. The volume distribution was obtained by calculating the volume for the i^{th} class from the number of particles in that class and the average particle volume for that class, as calculated from the mean diameter. As appears from data in Fig. 3, the particles of the 20% dispersion are, on the average, smaller than those of the 40% dispersion, although the size distribution is substantially independent of concentration, as shown by the similar shape of the respective volume and number distribution curves and the virtually equal values of the respective volume to number diameter ratio.

3.4. Studies on drug release from microspheres

In principle, reproducibility of release data from microspheres would require control of the

specific surface of the microsphere samples used in the experiments. This is a difficult condition to meet if small samples are taken from a whole of free-flowing particles of scattered sizes, due to the tendency of such a system to segregate. Therefore, each batch of microspheres was divided into sufficiently narrow size ranges, and samples taken from a specified range were used for each release test. This also allowed evidence of the effect of microsphere size on release kinetics. The 105–250, 355–425 and 500–710 μm ranges were tested. The following equation:

$$F = kt^n \quad (1)$$

proposed by Peppas, 1985, where F represents the dose fraction released in time t, k is a rate constant and the exponent, n, characterizes the kinetics type, has proven useful for the study of the release mechanism. The equation was fitted to experimental release data by a nonlinear data fitting computer program, using minimization of the χ^2 as the criterion of 'best fit' (Lu et al., 1996). The data for the 105–250 μm size range were not analyzed by Eq. (1), since they were deemed not sufficiently accurate, due to an exceedingly fast release. For the 355–425 and 500–710 μm ranges,

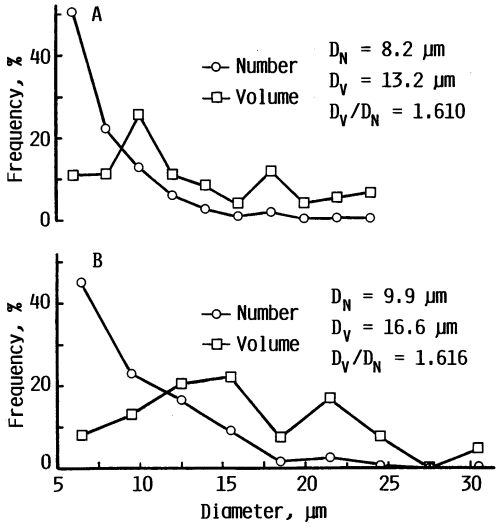

Fig. 3. Number and volume size distributions of PCP-NAM (4:1 w/w) particles dispersed in silicone at the 20% (a) or 40% (b) concentration, as determined by S.E.M. DN, mean number diameter; DV, mean volume diameter.

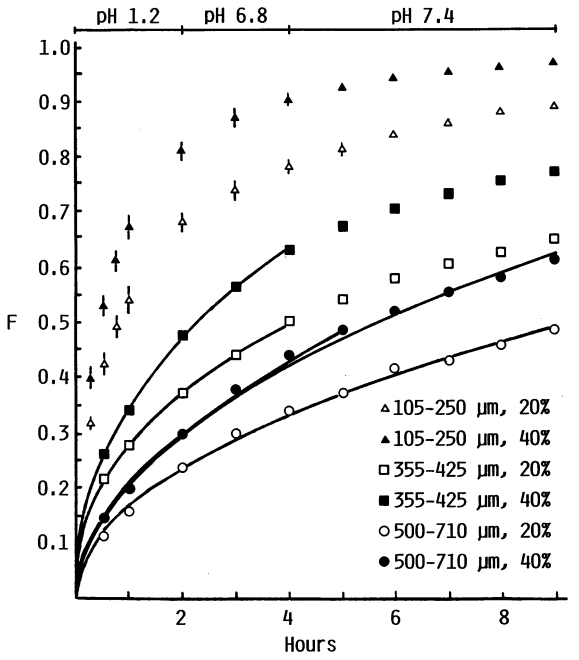

Fig. 4. Drug release (F = cumulative fraction released) vs. time data for microspheres in different size ranges, formulated with different PCP-NAM (4:1 w/w) concentrations. Each data point is the mean of three values. Where not shown, the S.D. bar falls within the symbol. Full lines are calculated from fitting of Eq. (1) to experimental points.

Fig. 4 shows a satisfactory fit of the calculated curves to data. To study the relevance of microsphere size to the release kinetics, values of the parameters in Eq. (1) were derived from the data plotted in the figure, up to the same F value for different size ranges of the same formulation, namely, up to $F \cong 0.5$, for the 20% dispersed phase concentration, or up to $F \cong 0.6$, for the 40% dispersed phase concentration. The relevance of dispersed phase concentration was evaluated through k and n values derived from data in Fig. 4 up to $F \cong 0.5$, for different concentrations and the same 500–710 μm size range. The calculated values are listed in Table 2. The differences between homogeneous values of the time exponent, n, for different size ranges or dispersed phase concentrations are not so clear as to state a substantial dependence of the apparent release kinetics on these variables. The somewhat lower n values for the smaller size might be due to some

Table 2
Parameters calculated from fitting of Eq. (1) to release data for microspheres in representative size ranges, containing different concentrations of dispersed PCP-NAM (4:1 w/w)

Dispersed phase concentration (%)	Size range (μm)	k (S.E.) h^{-n} from data up to		n (S.E.) from data up to	
		$F \cong 0.5$	$F \cong 0.6$	$F \cong 0.5$	$F \cong 0.6$
20	355–425	0.27 (0.00)		0.43 (0.02)	
	500–710	0.17 (0.01)		0.48 (0.02)	
40	355–425		0.35 (0.01)		0.44 (0.02)
	500–710	0.20 (0.01)	0.22 (0.01)	0.55 (0.02)	0.48 (0.02)

burst effect, as directly related to the specific surface of microspheres. In these circumstances, the parameter k can be used to quantify the effects of the above variables on release rate. In fact, a comparison between homogeneous k values indicates a clear dependence of release rate on microsphere size, probably as inversely related to the releasing surface, and a weak dependence of such a rate on dispersed phase concentration. None of the n values relative to $F \cong 0.5$, seen in Table 2, is substantially higher than 0.49, a value of n derived by Mc Neill and Graham (1996) from fitting of Eq. (1) to data on Fickian release from hydrogel spheres up to $F = 0.5$. Apparently, then, the release pattern for the present microspheres is different from the patterns for the silicone disk matrices described in previous reports, where the pH-sensitive swelling of the dispersed hydrogel produced a peak of release rate in intestinal fluid, in one case (Bilia et al., 1996), or release kinetics characterized by n values significantly higher than 0.5, in another (Buonaguidi et al., 1997). In order to account for such a difference, release from disk matrices containing in dispersion the same PCP-NAM (4:1 w/w) particles as the microspheres was studied. The advantage with the disks was in the possibility of measuring matrix swelling and drug release kinetics concurrently. Swelling and release data for disks containing 10, 20 and 40% dispersed phase are compared in Fig. 5. For the 10 and 20% concentrations, low matrix swelling and release rates, and an apparent concentration independence of release are observed. Such a concentration independence rules out a release via interconnected hydrogel particles, for these formulations, since release from a hydrophobic matrix via interconnected aqueous pores generated by a dispersed water carrier is known to imply a strong dependence of fractional release rate on carrier concentration (see, e.g., Carelli et al., 1987, 1989; Siegel et al., 1989). More likely, then, at the 10 or 20% concentration the osmotically active particles, although swelling, failed to interconnect,

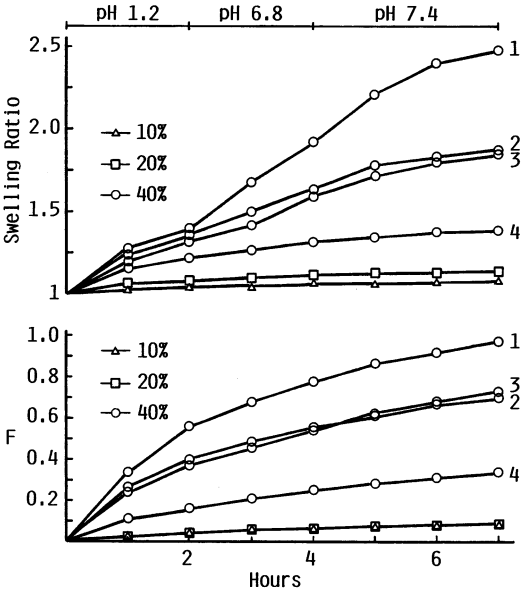

Fig. 5. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and drug release (F = cumulative fraction released) vs. time data for disk matrices formulated with different PCP-NAM (4:1 w/w) concentrations. The data for the 40% concentration are not reproducible, so the results of 4 runs are reported separately. The data for the 10 and 20% concentrations are the means of three runs. In these cases, the S.D. is always within the symbol.

so the release was controlled by partitioning and diffusion in the silicone continuum. This mechanism is supposed to apply as well to the microsphere formulation containing 20% dispersed phase. The disk matrices formulated with 40% PCP-NAM (4:1 w/w) are seen in Fig. 5 to swell and release the drug at much higher rates than those containing the lower dispersed phase concentrations, however, the data are not reproducible. With this formulation, the release via partitioning-diffusion in silicone must be paralleled by a more rapid release through an aqueous route created by interconnection of swollen hydrogel particles. However, the non-reproducible swelling and release data suggest a non-uniform distribution of the interparticle connections in the matrix volume. Interconnections to be created required cracking of the silicone polymer. As pointed out in previous papers (Carelli et al., 1995; Bilia et al., 1996), smaller hydrogel particles have a reduced cracking ability, so the present PCP-NAM particles, whose size was around one order of magnitude smaller than the granules used in the previous matrices, could only produce cracks in limited points, e. g., in some domains more crowded with particles. Once generated, a crack could propagate erratically in the matrix volume. Cracks connected to the matrix surface would make a preferential route for penetration of dissolution medium into and drug release from matrix. These arguments would account for both the lack of data reproducibility and the correspondence of faster swelling to faster release, appearing from the curves 1–4 of Fig. 5. When extending the above reasoning to the microspheres of the same formulation as the disk, it should be considered that a crack in the silicone polymer could not propagate further than the single microsphere wherein it originated. If the probability of a crack being initiated is admitted to be low, then only a minor fraction of microspheres in the sample used for the release test should be able to develop the aqueous route for release, so the release pattern, even for the microsphere formulation containing the higher concentration of osmotically active particles, should mainly be determined by partitioning and diffusion in silicone. This would explain the reproducibility of release data for the microspheres, as opposed to the lack of reproducibility with the disks.The above hypothesis on the release mechanism is consistent with the effect of doubling the concentration of the hydrogel particles on the release rate parameter, k, seen in Table 2. Such an effect, indeed, is rather weak if compared with the usual effect of porogen concentration on porous transport (Carelli et al., 1987, 1989; Siegel et al., 1989). Validity of the above hypothesis would also imply a weak influence of pH and ionic strength of dissolution medium on release. In fact, microsphere samples in the same size range, formulated with 40% PCP-NAM (4:1 w/w), when eluted 9 h with isotonic media of pH 1.2 or 7.4, or distilled water, yielded quite similar release data (not reported).

4. Conclusions

Although needing improvement, the present method of preparation has proven apt to yield non-clustered, free-flowing silicone microspheres in the 105–710 μm size range. The pH-sensitive hydrogel, PCP, medicated with NAM in the 4:1 PCP-NAM wt ratio, could be dispersed in the microspheres in the form of osmotically active particles of 8.2 and 13.2 μm mean number and volume diameter, respectively, for 20% dispersed phase, or 9.9 and 16.0 μm mean number and volume diameter, respectively, for 40% dispersed phase. No crystalline NAM could be detected by DSC in the medicated hydrogel. The small size of the dispersed hydrogel particles allowed a virtually 100% entrapment efficiency. The possibility of microspheres being sieve-sized to narrow ranges allowed reproducibility of release data and, in turn, assessment of reliable values of the time exponent characterizing the release kinetics. Such values, in conjunction with release and swelling data obtained from disk matrices of the same formulation as the microspheres, have substantiated the following hypothesis on the release mechanism. Due to their small size, the osmotically active particles have a limited ability to crack the silicone polymer and interconnect upon swelling, so the hydrogel route of drug release is of a minor

relevance, and so is the pH-sensitivity of the hydrogel. Drug release is mainly governed by partitioning-diffusion in the silicone continuum of matrix, therefore it is pH-independent and the time exponent is close to the value typical of Fickian release. It is concluded that a pH-controlled release pattern would require a larger size of dispersed hydrogel particles. However, larger particles might imply some difficulty in particle encapsulation. This problem is currently being addressed.

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References

Carelli, V., Di Colo, G., Nannipieri, E., Serafini, M.F., 1995. Evaluation of a silicone based matrix containing a crosslinked polyethylene glycol as a controlled drug delivery system for potential oral application. J. Control Release 33, 152–162.

Bilia, A., Carelli, V., Di Colo, G., Nannipieri, E., 1996. In vitro evaluation of a pH-sensitive hydrogel for control of GI drug delivery from silicone-based matrices. Int. J. Pharm. 130, 83–92.

Buonaguidi, M., Carelli, V., Di Colo, G., Nannipieri, E., Serafini, M.F., 1997. Evaluation of a pH-sensitive semi-interpenetrating polymer network for control of GI drug delivery. Int. J. Pharm. 147, 1–10.

Carelli, V., Di Colo, G., Nannipieri, E., 1987. Factors in zero-order release of clonidine hydrochloride from monolithic polydimethylsiloxane matrices. Int. J. Pharm. 35, 21–28.

Carelli, V., Di Colo, G., Guerrini, C., Nannipieri, E., 1989. Drug release from silicone elastomer through controlled polymer cracking: an extension to macromolecular drugs. Int. J. Pharm. 50, 181–188.

Chithambara Thanoo, B., Jayakrishnan, A., 1991. Tantalum loaded silicone microspheres as particulate emboli. J. Microencapsulation 8, 95–101.

Lee, P.I., Lum, S.K., 1992. Swelling-induced zero-order release from rubbery polydimethylsiloxane beads. J. Control. Release 18, 19–24.

Lu, D.R., Abu-Izza, K., Mao, F., 1996. Nonlinear data fitting for controlled release devices: an integrated computer program. Int. J. Pharm. 129, 243–251.

Maincent, P., Darmè, X., Kedzierewicz, F., Hoffman, M., Etienne, A., Lemut, J., 1995. Propanolol loaded silicone microspheres: preparation by emulsion-polymerization and in-vitro release rates. Proc. Int. Symp. Control. Rel. Bioact. Mater.. Control. Release Soc. Inc. 22, 432–433.

Mc Neill, M.E., Graham, N.B., 1996. Properties controlling the diffusion and release of water-soluble solutes from poly(ethylene oxide) hydrogel: 3. Device geometry. J. Biomater. Sci. Polym. Ed. 7, 937–951.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Remington: The Science and Practice of Pharmacy, 1995. 19th ed. Mack Publishing Company, Easton, pp. 1127.

Siegel, R.A., Kost, J., Langer, R., 1989. Mechanistic studies of macromolecular drug release from macroporous polymers. I. Experiments and preliminary theory concerning completeness of drug release. J. Control. Release 8, 223–236.

Sutinen, R., Laasanen, V., Paronen, P., Urtti, A., 1995. pH-Controlled silicone microspheres for controlled drug delivery. J. Control. Release 33, 163–171.

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