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Silicone microspheres for pH-controlled gastrointestinal drug delivery

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Abstract

Silicone microspheres containing pH-sensitive hydrogels are prepared, characterized and evaluated for their potential pH-controlled gastrointestinal (GI) drug delivery. The pH-sensitive hydrogels are semi-interpenetrating polymer networks (semi-IPN(s)) made of varying proportions of poly(methacrylic acid-co-methylmethacrylate) (Eudragit (EUD) L100 or EUD S100) and crosslinked polyethylene glycol 8000 (P8000C). Up to 35 wt% hydrogel particles of mean volume diameters from 89 to 123 μm, medicated with 15 wt% prednisolone (PDN), are encapsulated, with 100% efficiency, into morphologically acceptable silicone microspheres in the 500–1000 μm size range, by a modified emulsion vulcanization method. Microspheres are eluted for 9 h with isotonic fluids at pH values increasing from 1.2 to 7.4, to simulate transit across the GI regions. PDN release depends on dissolution medium pH and on hydrogel composition, which determines hydrogel pH-sensitivity. With the P8000C–EUD L100 (1:2) semi-IPN, the release shows a marked peak at pH 6.8. The P8000C–EUD S100 (1:2) semi-IPN causes a gastroprotection and an almost uniform distribution of released drug between media at pH 6.8 and 7.4. With the P8000C–EUD S100 (1:1) semi-IPN, the dose fraction released to gastric fluid increases to match the values for the media at pH 6.8 and 7.4. With the pH-insensitive, highly swelling, P8000C, the largest dose fraction is released to the gastric medium and release is of Fickian type. With semi-IPNs, release depends weakly on the buffer molarity of the dissolution medium, a reduction from 0.13 to 0.032 of which renders the release rate to the media at pH 6.8 and 7.4 more uniform. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Silicone; Microspheres; Semi-interpenetrating polymer networks; pH-sensitive hydrogel; Prednisolone; Oral delivery system

1. Introduction

In previous papers, disk-shaped silicone-based matrices for controlled release of different drugs

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to the gastrointestinal (GI) tract have been described (Bilia et al., 1996; Buonaguidi et al., 1997). With these systems, drug release was controlled by the pH-sensitive swelling of medicated hydrogel granules, dispersed in the matrix, which responded to the pH changes experienced during matrix transit across the GI tract with a swelling pattern apt to produce a progressive increase of the apparent drug diffusivity in the matrix, thereby providing an extended release in the intestinal region. In a further report, the possibility of obtaining a similar release pattern with a multiparticulate system was evaluated (Carelli et al. 1997), in view of the advantages this type of system offers over single unit systems, which include the possibility of combining various types of subunits in a single system, more reproducible transit times across the GI tract, and distribution over a vast surface area minimizing the risk of localized damage to the intestinal mucosa. Such a system consisted of silicone microspheres containing, in dispersion, medicated microparticles of Polycarbophil, a pH-sensitive hydrogel made of crosslinked polyacrylic acid. Polycarbophil was chosen because it is a commercial powder of small particle size (<20 μm), which allowed weight fractions of up to 40% to be entrapped into silicone microspheres of 105–710 μm size with virtually 100% efficiency. Nicotinamide was chosen as a model drug, since it was expected to dissolve–diffuse in the swelling-interconnecting hydrogel particles rather than in silicone, due to its high water solubility. Nevertheless, drug release was actually found to be governed by partitioning-diffusion in the silicone continuum of microspheres; therefore, it was pH-independent and of Fickian type. This behavior was ascribed to an excessively small size of the hydrogel particles, wherefore they were unable to crack the silicone polymer and interconnect upon swelling.

The present paper describes a successful attempt to prepare hydrogel-containing silicone microspheres able to realize a pH-sensitive hydrogel-controlled release pattern and, hence, to sustain the release rate in the intestinal region. pH-Sensitive hydrogels have been prepared by interpenetrating linear poly(methacyilic acid-co-methylmethacrylate), such as Eudragit (EUD) L100 or S100, into the hydrophilic network of crosslinked polyethylene glycol 8000 (P8000C). Reportedly, in such a semi-interpenetrating polymer network (semi-IPN), EUD and P8000C form an interpolymer complex via hydrogen bonding, which keeps the semi-IPN equilibrium swelling in water or acidic aqueous solution at a comparatively low level, depending on the P8000C–EUD proportion. In neutral aqueous buffer, the complex dissociates, due to ionization of EUD, which dissolves and diffuses out of the P8000C network. As a consequence, the swelling markedly increases and attains the equilibrium value for pure P8000C. These semi-IPNs allow modulation of pH-sensitivity via type and weight fraction of EUD in semi-IPN (Buonaguidi et al., 1997). The preparation method of microspheres was the same as that used previously (Carelli et al., 1997); however, the hydrogel particle size to be encapsulated in the present microspheres has been designed to be considerably larger than the Polycarbophil particles dispersed in the previous ones. Therefore, the present report also comprises a test of the method versatility. Prednisolone has been chosen as the model drug, because of its poor permeability through silicone rubber (Di Colo et al., 1986). Rhône-Poulenc's medical-grade silicone elastomer Silbione RTV 70141 has been used as the basic microsphere material. The term 'medical grade' implies biostability, biocompatibility, and the absence of systemic toxicity, which makes this silicone a candidate material for oral, as well as parenteral, controlled-release systems.

2. Materials and methods

2.1. Materials

The following commercially available materials were used as received. Prednisolone (PDN) (Carlo Erba, Milan, Italy), polyethylene glycol 8000 (PEG 8000) (Fluka Chemie, Buchs, Switzerland), 2 - ethyl - 2 - hydroxymethylpropane - 1,3 - diol (EHMPD) (Janssen, Beerse, Belgium), liquid paraffin (Olio di Vaselina, Carlo Erba), soft paraffin (Vaselina Filante, Carlo Erba), EUD L100 and EUD S100 (gifts from Rofarma Italia,

Milan, Italy), Silbione RTV 70141, composed of part A and part B (gift from Rhône-Poulenc Italia, Milan, Italy.

Tolylene-2,4-di-isocyanate (TDIC) (Janssen) was distilled under reduced pressure before use. According to the manufacturer, EUD L100 and EUD S100 are methacrylic acid/methyl methacrylate copolymers with free carboxyl/ester ratios of approximately 1:1 and 1:2, respectively. Silbione RTV 70141 is a two-component viscous-liquid medical-grade polydimethylsiloxane 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:

$$\equiv SiH + CH_2{=}CHSi\equiv \rightarrow \equiv SiCH_2CH_2Si\equiv$$

2.2. Preparation of P8000C

P8000C was prepared from PEG 8000 using EHMPD as the branching agent and TDIC as the crosslinking agent, as described previously (Carelli et al., 1993). The molar ratio of branching agent to PEG was 0.68, whilst the crosslinker was in the stoichiometric ratio to the hydroxyl functions of PEG and branching agent. The P8000C mass was made into granules by the technique described in a previous paper (Carelli et al., 1993). Portions of fully water-swollen polymer mass were thrust through 125 μm and, successively, 105 μm wire mesh. During extrusion, the polymer was maintained in contact with free water. Then, the excess water was decanted off and the water in the polymer particles was replaced by absolute ethanol, after which the particles were added to an excess of petroleum ether and finally dried under a stream of warm air.

2.3. Preparation of silicone microspheres

Dispersions (1 g) of 20–35% PDN-medicated semi-IPN particles in the silicone prepolymer were prepared by the following procedure. Weighed amounts of EUD L100 or EUD S100 were dissolved, together with the prescribed amount of prednisolone, in methanol-chloroform (9:1), and the solution was equilibrated overnight with a weighed amount of P8000C particles. The weight ratio of solution to particles was 7:1. Following equilibration, the solution was completely absorbed by the particles. The amounts were designed to obtain semi-IPNs of P8000C–EUD 1:1 or 1:2 weight ratios, medicated with 15% drug. In one case, EUD was absent, i.e. the P8000C particles were equilibrated with a solution containing only the drug. The swollen particles were added portionwise to a weighed amount of part A of the silicone prepolymer, while mixing with a spatula under a stream of warm air, until complete evaporation of the solvent. Solvent removal was considered complete when the mix attained a constant weight. Part B of 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, a procedure similar to that described in the previous report was followed (Carelli et al., 1997). The 1-g mix, immediately after degassing, was poured into a plastic tube equipped with a piston and, thereby, slowly injected into a fluid mass (50 g) of soft paraffin, contained in a beaker of 5 cm diameter, thermostated at 60°C, stirred at 220 rpm by a glass propeller of 4.5 cm diameter, operated by an overhead stirrer. Emulsification of the silicone mix took place in 20 s, after which the heating was removed and the stirring continued until the temperature dropped to around 50°C. The stirring was then stopped and the paraffin rapidly thickened by immediately immersing the emulsion in a water–ethylene glycol bath at −25°C, 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.

2.4. Check on silicone vulcanization

This check consisted of determining the weight fraction of material extractable from microspheres by a solvent, such as xylene, able to swell the crosslinked silicone and dissolve the uncrosslinked silicone. Weighed samples were immersed in excess xylene and kept for 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:

$$\frac{\text{(initial sample wt)} - \text{(dry extracted sample wt)}}{\text{(initial sample wt)} - \text{(dispersed phase wt in sample)}}$$

The dispersed phase weight in the sample could be calculated, knowing the drug weight in the sample (see Section 2.5) and the drug:hydrogel weight ratio. With all microsphere formulations, the calculated extractable fraction was $< 10\%$; therefore, the vulcanization was always considered satisfactory.

2.5. Release experiments

These experiments were carried out by the technique described in detail in a previous report (Carelli et al., 1997). Briefly, an accurately weighed (10^{-5} g) microsphere sample (20–40 mg) in the 500–710 or 850–1000 μm size range was stirred with 10 ml of dissolution medium at 37°C, under controlled hydrodynamics. At intervals, the dissolution medium was withdrawn by a syringe and replaced with the next fraction. Each fraction of dissolution medium was analyzed for the drug content. Sink conditions were maintained throughout the release experiment. If not otherwise indicated, samples were eluted with simulated GI 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 10 ml of methanol, in order to determine the initial drug content in the microspheres, as the sum of released and extracted amounts. Eight and 10 days at room temperature were sufficient for quantitative extraction of microspheres in the 500–710 and 850–1000 μm ranges, respectively, as shown by successive determinations.

The drug was assayed spectrophotometrically: the aqueous solutions at 246.8 nm, the methanolic ones at 242.0 nm. Blank runs demonstrated negligible interferences with the measurements.

2.6. Size analysis of P8000C and semi-IPN particles

Particle size analysis was carried out with a Reichert-Jung Microstar 120 projection microscope (American Optical, Buffalo, NY, USA). For analysis, the particles were suspended in part A of the silicone prepolymer. The suspension of the semi-IPN particles was prepared as described in Section 2.3. Analysis was made possible by the prepolymer clearness. For each sample, more than 300 particles were classified according to their projected diameter.

2.7. Morphology and size distribution of microspheres

The size distribution of microspheres in the 105–1000 μm range was determined by sieving. Sieves of 105, 250, 355, 425, 500, 710, 850 and 1000 μm mesh sizes were used. The morphology of microspheres was 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).

3. Results and discussion

3.1. Particle size of P8000C and semi-IPN

The size of the semi-IPN particles to be entrapped in the microspheres was controlled via the particle size of the precursor, P8000C. Fig. 1 shows the size distributions for the P8000C particles and the largest semi-IPN particles used in the present study, composed of P8000C–EUD (1:2) (the semi-IPN composition is hereafter expressed as the weight proportion of components). Either the number or volume distribution of the semi-IPN particles exhibits, in Fig. 1b, an increased frequency of the lower sizes, with respect to the corresponding distribution for the P8000C particles, shown in Fig. 1a. This results in a slight decrease of particle size homogeneity for the semi-IPN, as expressed by the ratio of number to volume mean projected diameters. This finding indicates that the semi-IPN preparation method could not ensure a perfectly homogeneous distribution of the EUD mass among the P8000C particles; in fact, the smaller particles absorbed a higher EUD weight fraction, by virtue of their higher specific surface.

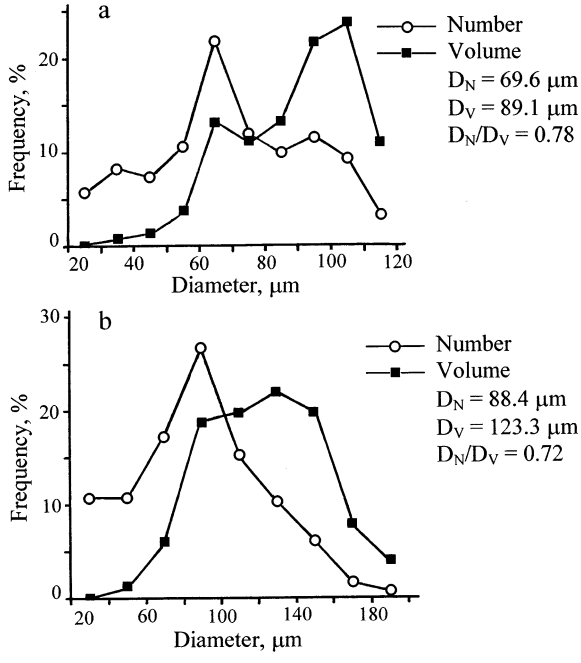

Fig. 1. Number and volume size distributions of P8000C (a) and P8000C–EUD (1:2) semi-IPN (b) particles. D_N and D_V, mean number and volume diameter, respectively.

3.2. Preparation of microspheres

When applied to the present formulations, the emulsion vulcanization technique described in the previous study (Carelli et al., 1997) led to substantially larger microspheres, presumably due to the larger size of the entrapped hydrogel particles ($\sim$120 vs $\sim$13 μm). Therefore, we had to cope with a considerably faster settling of the silicone droplets suspended in the fused paraffin, which occurred from the moment the stirring was stopped, to the moment the paraffin was completely thickened. In order to limit the droplet coalescence due to the settling, the volume of suspending medium was doubled, thus doubling the settling pathlength, and also, after emulsifying the silicone mix in the fused paraffin, the paraffin viscosity was raised by removing the heating and letting the temperature drop to 50°C, under stirring. At this temperature, the paraffin was still in the liquid state, although visibly more viscous. Then, the stirring was stopped and the paraffin rapidly solidified. The yield of the preparation, expressed as wt% of microspheres in the 500–1000 μm size range obtained from the total mass of silicone material recovered from the paraffin, is reported in Table 1 for microspheres formulated with 20, 25 and 35% hydrogel particles. Each formulation is characterized by the weight fraction of semi-IPN particles in the silicone matrix and EUD content in semi-IPN, irrespective of the EUD type. The yield values show an inverse relationship to the weight fraction of particles in the silicone matrix. Indeed, the yield for the nominal concentration of 20% is significantly higher than that for 35%, on the basis of the Student *t*-test. As an explanation of such a relationship, the subdivision of the silicone prepolymer mix into microspheres smaller than 1000 μm is supposed to be easier with lower weight fractions of dispersed phase in such a mix, due to a lower bulk viscosity. On the other hand, for a given weight

Table 1
Yield of preparation and entrapment efficiency for silicone microspheres containing different concentrations of hydrogel particles of different composition

Hydrogel composition (w:w)[a]	Hydrogel concentration (wt%)	Yield (S.D.) (%)[b,d]	Size range of microspheres (μm)	Entrapment efficiency (S.D.)[c,d]
P8000C–EUD (1:2)	20	77.6 (10.5)	500–710	1.3 (0.1)
			850–1000	1.2 (0.2)
	25	61.5 (6.7)	500–710	1.1 (0.1)
			850–1000	1.1 (0.0)
	35	42.1 (4.0)	500–710	1.1 (0.0)
			850–1000	1.1 (0.0)
P8000C–EUD (1:1)	25	52.6 (8.5)	500–710	1.1 (0.0)
			850–1000	1.1 (0.0)
	35	37.0 (7.9)	500–710	1.2 (0.1)
			850–1000	1.1 (0.1)

[a] P8000C–EUD proportion, irrespective of EUD type.
[b] Wt% of microspheres in the 500–1000 μm size range, based on the mass of silicone material recovered from the paraffin.
[c] Ratio of experimental to theoretical drug load in microspheres.
[d] Mean and S.D. of three preparations.

fraction of the dispersed phase, a change of dispersed particle size, as associated with a change in semi-IPN composition, appears, from Table 1, to cause no significant yield variation. In Table 1 is also found, for representative size ranges of each formulation, the entrapment efficiency, expressed as the ratio of experimentally determined to theoretical drug load in microspheres. The latter was calculated without considering the contribution of the talc adsorbed on the microsphere surface to the microsphere weight. It will be shown later that such a contribution was indeed negligible. As it is observed, the entrapment efficiency is always slightly greater than unity. Such high values are indicative of a virtual absence of drug partitioning from microspheres into the suspending medium and/or the washings, and also, of a preferential wetting of the semi-IPN particles by silicone, rather than by paraffin. The significant, although small, deviation in excess of 100% efficiency, seen in all cases in Table 1, is ascribed to a loss of silicone from the fluid silicone-semi-IPN mix, due to adherence to glass surfaces. A similar demixing has already been reported (Buonaguidi et al., 1997). As the relevant data in Table 1 show, the entrapment efficiency is the same for microspheres of different size ranges and semi-IPN compositions.

3.3. Size distribution of microspheres

Fig. 2 shows the size distributions of microspheres having representative formulations. It is seen that the major contribution to the weight of the microspheres recovered is given in all cases by the fraction in the 500–1000 μm range. For a given weight fraction of semi-IPN particles in microspheres, a change of particle size, associated with a change in semi-IPN composition, produces

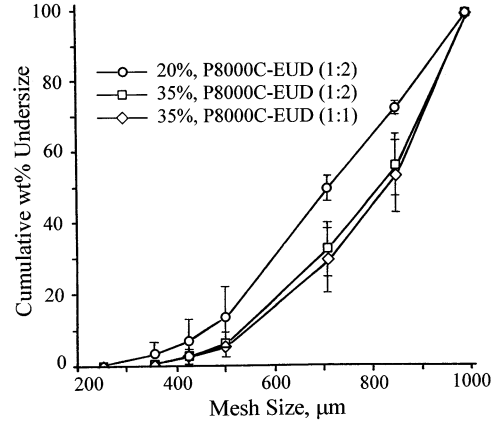

Fig. 2. Size distribution of silicone microspheres formulated with different weight fractions of semi-IPN particles of different composition. Mean and S.D. for three batches.

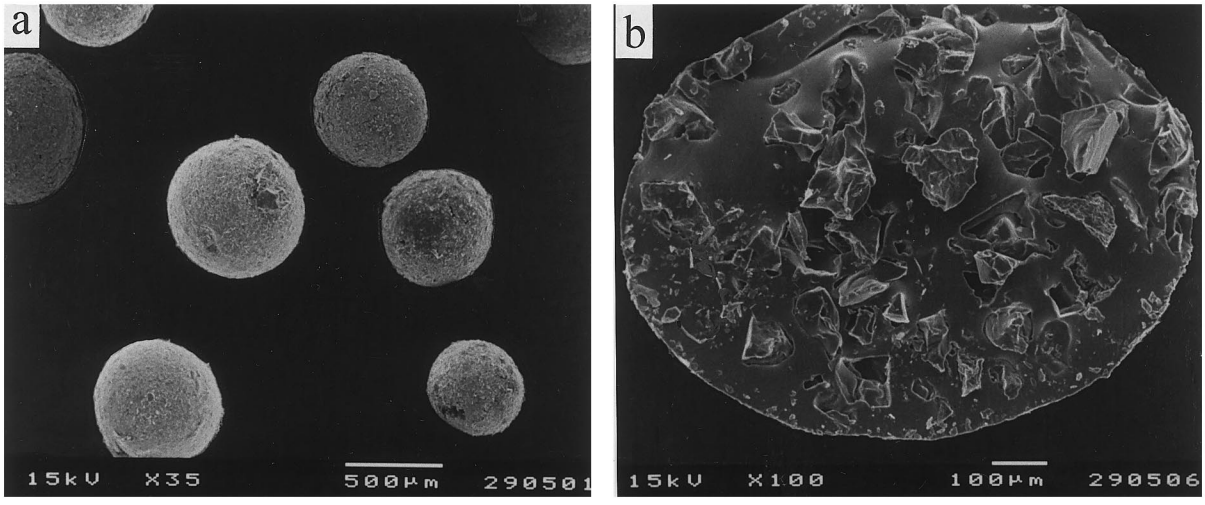

Fig. 3. SEM micrographs showing the external (a) and internal (b) morphology of microspheres.

no appreciable effect on the size distribution of microspheres. Conversely, such a distribution is affected by a change in weight fraction of semi-IPN particles in microspheres, the percentage of the lower sizes being increased by a decrease of such a weight fraction. This effect is ascribed to a decreased bulk viscosity of the silicone prepolymer mix, associated with a lower hydrogel concentration, allowing a higher degree of subdivision of the mix in the fused paraffin.

3.4. Morphology of microspheres

The SEM micrograph in Fig. 3a evidences the virtually spherical shape of microspheres containing 35% semi-IPN particles of the size distribution shown in Fig. 1b. When the weight fraction or the size of semi-IPN particles was increased over these limits, elongated masses were obtained, at the surface of which, hydrogel particles not fully covered by silicone could be evidenced by SEM (not reported). The rough surface of microspheres in Fig. 3a is due to adsorbed talc, used to improve the microsphere flowability. Sections of microspheres were cut with a sharp blade, in order to examine the distribution of the entrapped hydrogel particles. The SEM micrograph of a typical cross-section is shown in Fig. 3b. As is observed, the shape of the larger microsphere, from which the section was taken, tends to turn slightly oval. It is of note that the blade could sharply cut the silicone, but not the harder hydrogel particles, which were, in some cases, extracted from silicone. Also, the invasive technique brought some talc particles to be adsorbed on the surface of the microsphere section examined. Nevertheless, Fig. 3b gives a clear indication of a random distribution of the semi-IPN particles within the microspheres. A negligibly small thickness of the talc layer adsorbed on the microsphere external surface also appears in Fig. 3b.

3.5. Drug release from microspheres

As explained in our previous report (Carelli et al., 1997), the reproducibility of release data could be improved by dividing each microsphere batch into narrow size ranges, and using, for each release test, samples taken from a specified range. In the present study, the 500–710 and 850–1000 μm ranges were taken as representative of the whole 500–1000 μm range. The rate vs time profile for microspheres of whatever size within the 500–1000 μm range, is supposed to be between the profiles determined for the 500–710 and 850–1000 μm ranges.

3.5.1. Microspheres containing semi-IPN

The release rate vs time profiles for microspheres formulated with 25% semi-IPN particles of different composition are presented in Figs. 4 and 5. Each data point represents the dose fraction released in a 1-h interval after time t, and is placed at time $t+0.5$ h. The dose fractions released from microspheres of different formulation to dissolution media of different pH values, during the simulated transit across the GI regions, are found in Table 2. The release from microspheres formulated with the semi-IPN having P8000C–EUD (1:2) composition is strongly pH-dependent. Indeed, as seen in Fig. 4, the release rate at pH 1.2 is comparatively low, then it peaks during the first hour of elution at pH 6.8. This behavior is a direct consequence of the pH effect on semi-IPN swelling, and also, of the tendency of PDN to dissolve-diffuse in the swollen-interconnected hydrogel particles, rather than partition-

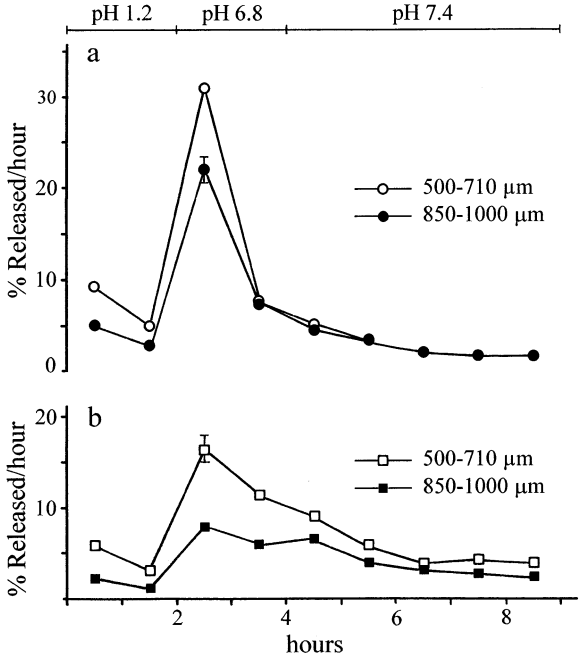

Fig. 4. Fractional release rate vs time profiles for microspheres in different size ranges, formulated with 25 wt% semi-IPN particles of P8000C–EUD L100 (1:2) (a) or P8000C–EUD S100 (1:2) (b) composition. Particles are medicated with 15 wt% PDN. Each data point is the mean of three values. Except for a few cases, the S.D. bar falls within the symbol.

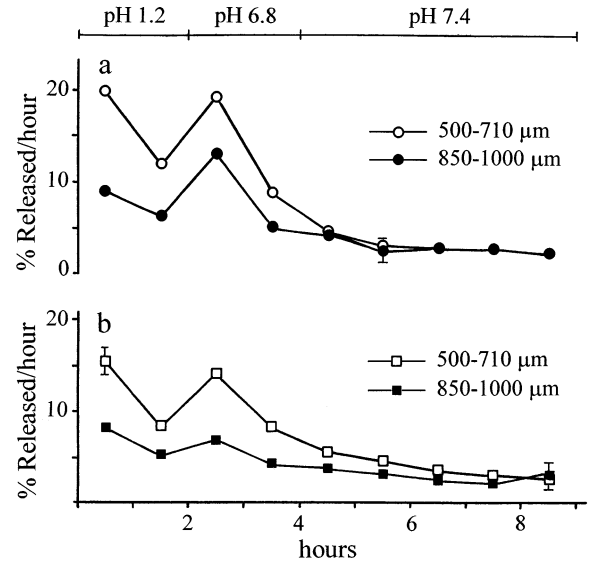

Fig. 5. Fractional release rate vs time profiles for microspheres in different size ranges, formulated with 25 wt% semi-IPN particles of P8000C–EUD L100 (1:1) (a) or P8000C–EUD S100 (1:1) (b) composition. Particles are medicated with 15 wt% PDN. Each data point is the mean of three values. Except for a few cases, the S.D. bar falls within the symbol.

diffuse in the silicone continuum (Di Colo et al., 1986; Bilia et al., 1996). Data on the pH effect on equilibrium swelling of the semi-IPNs containing EUD L100, expressed as ratio of swollen to initial dry weights, could be derived from Buonaguidi et al. (1997). For the P8000C–EUD L100 (1:2) composition, which produces the highest rate peak at pH 6.8, seen in Fig. 4a, such a swelling ratio is around 2, at pH 1.2, and around 6, at pH > 6. To note that the latter value is calculated as one-third of the equilibrium swelling ratio for the pure P8000C in water, since the P8000C–EUD L100 (1:2) composition turns into pure P8000C, at pH > 6, due to EUD L100 dissolution and exit from the P8000C network (Buonaguidi et al., 1997). For the hydrogel of P8000C–EUD L100 (1:1) composition, equilibrium swelling ratio values of around 4, at pH 1.2, and around 9, at pH > 6, could similarly be derived. Such a difference in pH-responsiveness with respect to the P8000C–EUD L100 (1:2) composition results in a different release rate vs time profile, which shows, in Fig. 5a, higher rates during the elution at pH

Table 2
Dose fraction released from microspheres of different size ranges, containing different weight fractions of hydrogels of different compositions, to media at increasing pH, simulating transit across different regions of the GI tract

Hydrogel composition (w:w)	Hydrogel weight fraction (%)	Size range (μm)	Dose fraction released[a]			
			pH 1.2 (2 h)	pH 6.8 (2 h)	pH 7.4 (5 h)	total (9 h)
P8000C–EUD L100 (1:2)	25	500–710	14.6 (0.1)	39.8 (0.0)	17.3 (0.8)	71.7 (0.8)
		850–1000	8.3 (0.9)	30.8 (2.2)	16.8 (1.1)	55.9 (4.1)
P8000C–EUD L100 (1:1)		500–710	31.9 (2.1)	28.1 (0.7)	10.4 (2.9)	70.4 (0.4)
		850–1000	15.3 (1.7)	18.1 (1.2)	15.3 (0.5)	48.7 (1.8)
P8000C–EUD S100 (1:2)		500–710	9.1 (0.1)	28.0 (0.8)	27.2 (0.9)	64.3 (1.5)
		850–1000	3.8 (0.1)	14.3 (0.2)	19.9 (0.7)	38.0 (0.6)
P8000C–EUD S100 (1:1)		500–710	23.4 (1.2)	22.9 (0.3)	19.4 (1.3)	65.7 (3.4)
		850–1000	13.4 (0.7)	12.0 (0.6)	15.0 (0.2)	40.4 (0.5)
P8000C		500–710	36.0 (0.3)	10.4 (0.1)	13.6 (0.1)	60.0 (0.1)
		850–1000	20.5 (0.9)	7.4 (0.3)	10.4 (0.6)	38.3 (1.8)
P8000C–EUD L100 (1:2)	35	500–710	25.2 (0.4)	49.5 (1.0)	22.2 (1.3)	96.9 (1.8)
		850–1000	11.6 (1.1)	37.0 (0.7)	22.2 (0.9)	70.8 (1.4)
P8000C–EUD L100 (1:1)		500–710	38.9 (1.0)	25.9 (0.7)	17.7 (0.6)	82.5 (0.9)
		850–1000	22.9 (0.8)	19.3 (0.1)	20.3 (0.1)	62.5 (0.8)
P8000C–EUD S100 (1:2)		500–710	17.8 (0.9)	36.7 (0.3)	27.6 (0.9)	82.1 (0.3)
		850–1000	8.9 (0.4)	22.4 (0.3)	27.2 (0.3)	58.5 (0.4)
P8000C–EUD S100 (1:1)		500–710	36.1 (1.2)	25.2 (0.5)	23.2 (0.7)	84.5 (0.0)
		850–1000	19.4 (0.1)	18.0 (0.1)	23.0 (0.7)	60.4 (0.7)

[a] Mean (S.D.) of three runs.

1.2 and a less pronounced rate peak at pH 6.8. Fig. 4b and Fig. 5b show the release rate vs time profiles generated by semi-IPNs containing EUD S100, in place of EUD L100. A comparison of these profiles with the corresponding ones in Fig. 4a and Fig. 5a shows that, for a given P8000C–EUD proportion, EUD S100 generates lower rate peaks, compared with EUD L100. Indeed, the former is known to be more hydrophobic than the latter, which can cause a slower hydration and ionization of the former, resulting in a slower swelling of the semi-IPN particles.

It is seen, in Table 2, that the dose fractions released in 9 h from the microsphere formulations discussed so far, containing 25% semi-IPN particles, are between 64 and 72% and 38 and 56%, for the 500–710 and the 850–1000 μm size ranges, respectively. The table also shows that such fractions increase to 82–97 and 58–71%, respectively, when the semi–IPN concentration in microspheres is increased to 35%. For a given semi-IPN composition, the increase in released dose fraction is distributed among the receiving media of different pH, in such a way that the overall release pattern is not substantially altered. Thus, with either 25 or 35% semi-IPN in microspheres, the P8000C–EUD S100 (1:2) composition exerts a gastroprotective effect, followed by a fairly uniform distribution of the released fraction between the media at pH 6.8 and 7.4, while, with the P8000C–EUD S100 (1:1) composition, the dose fraction released to the gastric medium increases

to match the values for the media at pH 6.8 and 7.4. Of the two EUD types, EUD L100 produces the higher cumulative fraction released in 9 h and the higher release peak at pH 6.8.

3.5.2. Microspheres containing P8000C

The release profile for microspheres formulated with the pH-insensitive, highly swelling P8000C was determined and compared with the profiles generated by the semi-IPNs, in order to better appreciate the relevance of hydrogel pH-sensitiveness. As shown by the relevant data in Table 2, with pure P8000C in microspheres, a preponderant dose fraction is released to the gastric medium, which evidences a clear difference in release pattern with respect to the formulations containing semi-IPNs of whichever composition. The following well known equation (Peppas, 1985)

$$F = k\,t^n \quad (1)$$

where F represents the dose fraction released in time t, k is a rate constant and the exponent, n characterizes the kinetics type, was fitted to experimental F vs t data by a nonlinear data fitting computer program, using minimization of χ^2 as the criterion of 'best fit' (Lu et al., 1996). The n values obtained from the fitting, seen in Fig. 6, are close to 0.49, a value of n typical of a purely diffusive release from a sphere up to $F = 0.5$, with constant diffusivity (McNeill and Graham, 1996). It is therefore reasoned that the swelling of the P8000C particles within the microspheres is much faster than release, so the apparent drug diffusivity in the matrix attains a virtually constant value before a significant dose fraction has been released.

3.5.3. Effect of buffer molarity of dissolution medium

In principle, the release rate depends on the rate of buffer salt diffusion from the dissolution medium into the semi-IPN, so far as hydrogel swelling depends on EUD ionization. Ultimately, the release rate can depend on the buffer molarity of dissolution medium. In order to test such an effect, microspheres formulated with the P8000C–EUD S100 (1:2) semi-IPN

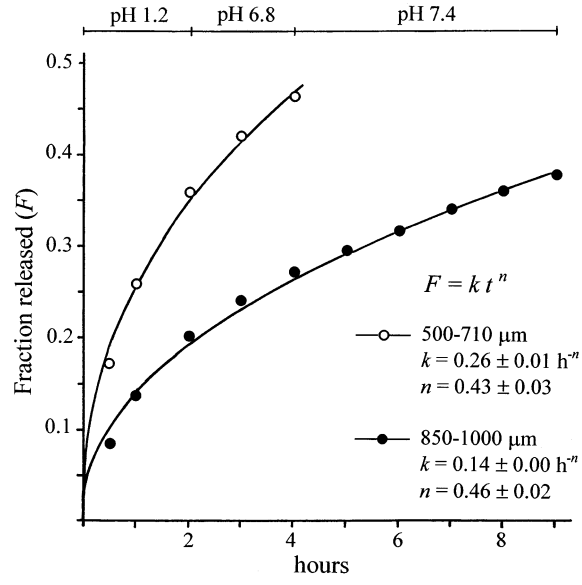

Fig. 6. Fitting of Eqn. 1 to release data for microspheres in different size ranges, formulated with 25 wt% P8000C particles medicated with 15 wt% PDN. Each data point is the mean of three values. In all cases, the S.D. bar falls within the symbol.

have been eluted with 0.13 or 0.032 M buffers. Fig. 7 indeed shows a more uniform release rate with the buffers of lower molarity, which are supposed to produce slower EUD ionization and hydrogel swelling.

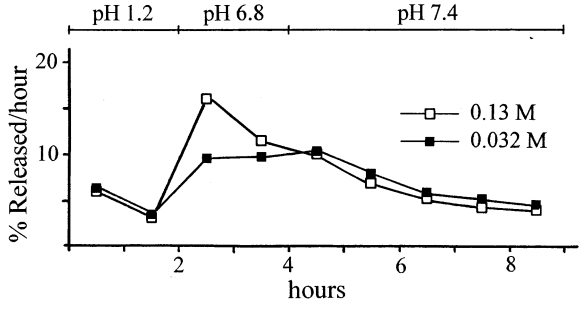

Fig. 7. Effect of molarity of buffers at pH 6.8 and 7.4 on the release rate vs time profile of microspheres in the 710–850 μm size range, formulated with 35 wt% semi-IPN particles of P8000C–EUD S100 (1:2) composition. Particles are medicated with 15 wt% PDN. Each data point is the mean of three values. In all cases, the S.D. bar falls within the symbol.

4. Conclusions

The present method of preparation of microspheres has allowed encapsulation of up to 35 wt% medicated hydrogel particles of mean volume diameters from 89 to 123 μm into morphologically acceptable silicone microspheres in the 500–1000 μm size range, with an entrapment efficiency of 100%. PDN release from microspheres to simulated GI fluids depends profoundly on the composition of the entrapped hydrogel, which determines the hydrogel pH-sensitiveness. Then, a potential advantage of the present system resides in the possibility of obtaining different drug release patterns by simply varying the P8000C–EUD ratio and/or the EUD type, with no impact on the microsphere size distribution nor on the preparation procedure. Thus, with pure P8000C as the hydrogel, a preponderant dose fraction should be released to the stomach: with the P8000C–EUD S100 (1:2) semi-IPN, the microsphere system should perform a gastroprotection, followed by a fairly uniform release to the intestine; and with the P8000C–EUD S100 (1:1) semi-IPN, the system should release the drug to the whole GI tract at slowly declining rates. The present release patterns, obtained with PDN as the model drug, show promise to be extended to other drugs with different solubilities, provided they are released from microspheres via the pathway generated by the swollen interconnected hydrogel particles. Indeed, a weak dependence of release data on drug solubility has already been reported for planar silicone matrices containing dispersed granules of a pH-sensitive hydrogel, composed of interpenetrating crosslinked PEG and polymethacrylic acid (Bilia et al., 1996). Such a virtually drug-independent release has been ascribed to the high solubilizing power of PEG. The release profile generated by a semi-IPN can be influenced by the buffer molarity of dissolution medium. However, it has been shown, using microspheres formulated with the P8000C–EUD S100 (1:2) semi-IPN, that the effect of a reduction of molarity from 0.13 to 0.032 is modest and acts to render the release rate to the media at pH 6.8 and 7.4 more uniform. These findings suggest that a difference in buffering power between the simulated and the actual GI fluids should be responsible of no important differences between in vitro and in vivo release. Despite the alleged chemical and biological inertness of the polymers used in the microsphere formulations, the issue concerning the toxicity of residues from incomplete vulcanisation and purification of microspheres remains open. Facing such problems should be part of the developmental work.

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