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Evaluation of a pH-sensitive semi-interpenetrating polymer network for control of GI drug delivery

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Abstract

The ability of a pH-sensitive semi-interpenetrating polymer network (semi-IPN), composed of crosslinked polyethylene glycol 8000 (P8000C) and Eudragit L100 (EUD), to control the release of drugs having very different aqueous solubilities, such as nicotinamide (NAM) and salicylamide (SAM), from silicone-based matrices to simulated GI fluids, is evaluated in vitro. P8000C and EUD form an interpolymer complex through hydrogen bonding. The semi-IPN equilibrium swelling in simulated gastric fluid (SGF) depends inversely on the EUD fraction in the complex. In simulated intestinal fluid (SIF) the P8000C-EUD complex dissociates, EUD dissolves and diffuses out of the P8000C network and the swelling markedly increases. Drug release from 1-mm thick silicone disk matrices containing, in dispersion, around 35 wt% medicated semi-IPN granules is studied by eluting matrices with SGF for 2 h, followed by SIF for 7 h. Increasing EUD fractions in semi-IPN decrease the release rate in SGF and tend to linearize the overall release profile. Pseudo-zero order release, for either NAM or SAM, is obtained with semi-IPN granules composed of P8000C/EUD 1:2. The fractional release rate shows limited dependence on the dose, in the 5–20% range of drug loads in granules, and on the drug type. Dose fractions in between 50% and 80% are released in 9 h. Drug release is virtually uninfluenced by ample variations in osmolality, ionic strength and buffer molarity of dissolution medium. © 1997 Elsevier Science B.V.

Keywords: Silicone matrix; pH-sensitive hydrogel; Semi-interpenetrating polymer network; Interpolymeric polycarboxylic acid-polyether complex; Oral drug delivery system; Nicotinamide

1. Introduction

Until the early nineties silicone elastomer has been used to construct prolonged-release matrices

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intended for implantation or insertion into body cavities. Very recently, the present authors have described silicone-based controlled-delivery matrices with a potential for oral application (Carelli et al., 1995; Bilia et al., 1996). The basic system consisted of a 1-mm thick silicone disk containing, in dispersion, around 35 wt% medicated granules of a crosslinked hydrogel. Following matrix contact with simulated GI fluids (SGIF), the hydrogel granules in matrix would swell, connections among granules would be formed and/or enlarged by the swelling, thus developing an interconnected hydrogel phase whereby the drug contained in the granules could dissolve and diffuse out of matrix. The hydrogel swelling pattern was determinant to the drug release pattern. In fact, when the environmental pH was varied to simulate matrix transit across the GI tract, a hydrogel endowed with a high swelling degree in simulated gastric fluid (SGF) promoted the release to this fluid of around half the dose of clonidine HCl or salicylamide in 2 h (Carelli et al., 1995), whereas the dose fractions of clonidine HCl, salicylamide, nicotinamide or prednisolone released to SGF were small compared to those released to simulated intestinal fluid (SIF), when a pH-sensitive hydrogel having low swelling degree in SGF, high in SIF, was used (Bilia et al., 1996). The former hydrogel yielded $\sqrt{t}$-type release kinetics, the latter produced two peaks of release rate, a lower one in SGF, a higher one in SIF, both followed by a rapid decline of rate.

The aim of the present work was to develop a pH-sensitive hydrogel which, once formulated within a silicone matrix of the above type, could respond to the pH variations experienced during matrix transit across the GI tract, with a swelling pattern appropriate to extend drug release in the intestinal tract and, at the same time, to control the release kinetics to a pseudo-zero order. In this prospect, a semi-interpenetrating polymer network (semi-IPN), composed of a crosslinked polyethylene glycol (PEG) with a high equilibrium swelling degree in water, and an interpenetrating water-insoluble polycarboxylic linear polymer, such as Eudragit L100 (EUD), was considered a promising starting material. In principle, the swelling pattern of the semi-IPN in GI fluids and, hence, the pattern of drug release from matrix to such fluids, could be modulated by varying the PEG-EUD ratio in the semi-IPN. This paper describes an evaluation of the above rationale, using nicotinamide and salicylamide as models of freely and barely water-soluble drugs, respectively.

2. Materials and methods

2.1. Materials

The following commercially available materials were used as received.

Salicylamide (SAM), polyethylene glycol (PEG) 8000 and, α,α'-azobis-(isobutyronitrile) (AIBN) (Fluka Chemie AG, Buchs, Switzerland), nicotinamide (NAM) (Sigma, St. Louis, MO, USA), 2-ethyl-2-hydroxymethylpropane-1,3-diol (EHMPD) (Janssen, Beerse, Belgium), Eudragit L100 (EUD) (gift from Rofarma Italia S.r.l., Milano, Italy), Silbione RTV 70141, composed of part A and part B (gift from Rhône-Poulenc Italia S.p.A., Milano, Italy).

EUD is a methacrylic acid/methyl methacrylate copolymer with a free carboxyl to ester groups ratio of approximately 1:1. 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.

Tolylene-2,4-diisocyanate (TDIC) (Janssen, Beerse, Belgium) was distilled under reduced pressure before use.

The EUD sodium salt was prepared by gradually adding a 0.25 N NaOH solution to a suspension of 1 g EUD in 100 ml water under stirring, until a clear solution of pH 7 resulted. During the addition, the pH was never allowed to exceed 7.2. The water was then evaporated under reduced pressure and the resulting EUD sodium salt was vacuum dried.

2.2. Preparation of semi-interpenetrating polymer network (semi-IPN) granules

Crosslinked PEG 8000 (P8000C) was prepared 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 crosslinked polymer mass was made into granules by the technique described in the previous paper (Carelli et al., 1993). Portions of fully water-swollen polymer mass were thrust twice through 800 μm wire mesh. The water in granules was replaced by absolute ethanol, then the granules were added to an excess of petroleum ether and finally dried under a stream of warm air. The granules were sieve sized to the 355–425 μm range. EUD was introduced into the P8000C network to obtain a semi-IPN of specified P8000C-EUD weight ratio, via impregnation of P8000C granules with an EUD solution in methanol/chloroform (9:1) of appropriate concentration. The solvent-P8000C weight ratio was always around 7. Upon equilibration in a sealed glass vessel for 24 h, the solution was completely absorbed by the granules. Subsequently, the solvent was let to evaporate in the ambient atmosphere, then the drying was completed under vacuum at 50°C. The dry semi-IPN granules were cohesive. In one case, the EUD sodium salt, instead of EUD, was added to P8000C, in the 1:1 weight ratio, by the above procedure, using methanol as the solvent.

2.3. Determination of swelling of semi-IPN granules

Dry semi-IPN granules (30–60 mg) were suspended in a large excess of the designed medium and the suspension was kept at 37°C for a measured time interval (for determination of equilibrium swelling, such a time was over 24 h), after which the major portion of liquid was decanted off; the remaining suspension was sucked into a plastic tube by means of a piston; the granules were let to settle on the piston; the surnatant liquid was expelled from the tube by pushing the piston; the wet granules were rapidly pushed between blotting paper and rapidly blotted dry; the major granule portion was transferred to a weighing bottle by a single stroke of a spatula and accurately weighed (sensitivity $< 10^{-4}$ g). The time of granule contact with the open air was around 5 s. Subsequently, the weighed granules were air dried, then vacuum dried, then weighed again. Granule swelling was quantified as the swollen to dry weights ratio (swelling ratio).

2.4. Preparation of matrices

Medicated semi-IPN granules were obtained by introducing the appropriate NAM or SAM concentration into the EUD solution used to prepare the semi-IPN. The granules were dispersed in the silicone prepolymer, the dispersion was degassed, prevulcanized, shaped into 1-mm thick sheets and vulcanized by quite the same procedure as that described previously (Bilia et al., 1996). Disks of 8 mm diameter were cut from the vulcanized sheets. All disks were elastic and their surfaces were smooth, non-tacky and hydrophobic. The nominal weight fraction of medicated granules in matrix was 27%, whereas the real value, as assessed via determination of the drug content in matrix, was $35.2 \pm 2.5\%$ ($n = 50$). Such a difference was due to some demixing of the granule-prepolymer mixture, which occurred during the matrix fabrication process.

2.5. Kinetic measurements

The procedure for simultaneous determination of the kinetics of drug release from matrix and of matrix swelling was the same as that reported previously (Bilia et al., 1996). The matrix was weighed (dry weight), then it was shaken in a known volume of elution medium at 37°C. Hourly, the matrix was withdrawn, quickly blotted dry, weighed (swollen weight), and immersed in the next fraction of fresh dissolution medium. The drug content in each fraction of dissolution medium was determined. The matrices were eluted for 9 h. If not otherwise indicated, simulated GI fluids (SGIF), consisting of the isotonic media B (simulated gastric fluid, SGF), E and I (simulated

Table 1
pH, osmolality, ionic strength and buffer molarity of aqueous media used for swelling and/or release studies[a]

Medium	pH	Osmolality[b] (mOsmol/kg)	Ionic strength	Buffer molarity
A	1.5	172	0.077	0.040
B	1.2	306	0.154	0.080
C	1.2	563	0.308	0.080
D	6.9	180	0.137	0.065
E	6.8	310	0.275	0.130
F	6.8	308	0.184	0.032
G	6.7	588	0.429	0.130
H	7.5	165	0.172	0.068
I	7.4	292	0.344	0.130
J	7.5	302	0.201	0.032
K	7.3	572	0.498	0.130

[a] For composition of media, see Bilia et al., 1996.
[b] As measured by an osmometer.

intestinal fluid, SIF), described in Table 1, were used in sequence for the elution, media B and E for 2 h each, medium I for the remaining 5 h. Following elution, the matrices were fully depleted of drug by extracting with ethanol/water (1:1), in order to determine the initial drug and granule content. Both NAM and SAM were assayed spectrophotometrically, as described in the previous paper (Bilia et al., 1996).

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 10–100°C temperature interval, at a heating rate of 10 K/min. The measuring cell worked in a freezer.

3. Results and discussion

3.1. Characterization of semi-IPN

Samples of semi-IPN granules containing varying P8000C-EUD ratios were equilibrated with an acidic aqueous solution (solution B, see Table 1) at 30°C and their equilibrium swelling was measured and plotted vs. the EUD weight fraction in the semi-IPN. As Fig. 1 shows, the semi-IPN swelling ratio decreases with increasing EUD fraction. Since EUD is hydrophobic, the EUD mass in the semi-IPN is indeed expected to give no contribution to the swelling. However, the swelling ratio for any EUD fraction is seen in Fig. 1 to be well below the value calculated from the following equation, which considers the

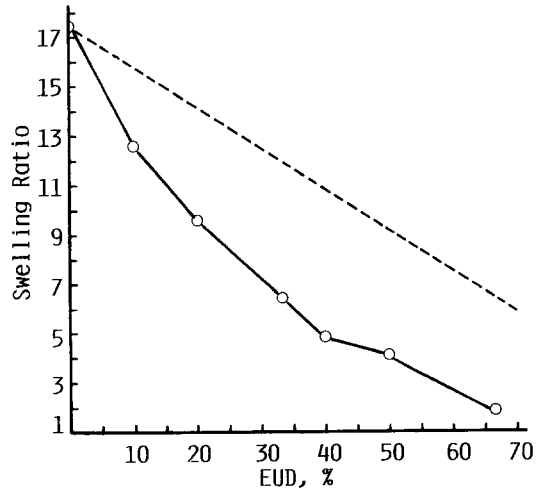

Fig. 1. Equilibrium swelling ratio of semi-IPN granules of varying composition, swollen in medium B, plotted vs. EUD wt fraction in semi-IPN. The dashed line is the plot for the swelling ratio as calculated from Eq. (1). Each data point is the mean of three samples. The range is always within the symbol.

swelling of P8000C in the semi-IPN unaffected by EUD:

$$S_s = S_P F_P + F_E \quad (1)$$

In Eq. (1), S_s and S_P represent the equilibrium swelling ratio of the semi-IPN and the pure P8000C, respectively, and F_P and F_E represent the weight fraction in the semi-IPN of P8000C and EUD, respectively.

This finding points to an interaction between P8000C and EUD, limiting the P8000C ability to swell. Indeed, interpolymeric complexes resulting from the interaction between polycarboxylic and polyether macromolecules have extensively been described (see, e.g., Bekturov and Bimendina, 1981; Bednar et al., 1984; Nishi and Kotaka, 1985; Lee, 1991; Bilia et al., 1996). The relevance of hydrogen bonding to the P8000C-EUD interaction was investigated by means of DSC, by comparing the effects of EUD and the EUD sodium salt on the P8000C crystalline melting. For the pure P8000C, crystalline melting in the 30–80°C interval, a peak temperature of 58.3°C and an enthalpy of fusion of 122.4 J/g were reported (Carelli et al., 1993). When EUD was introduced into the P8000C network in the 1:1 weight ratio, the enthalpy of fusion per unit P8000C mass dropped to 15.2 J/g, whilst the peak temperature was lowered to 49.6°C. Thus, the interaction of P8000C with the interpenetrating EUD nearly annihilated the P8000C crystallinity. On the other hand, the EUD salt, when added to the P8000C network by the same procedure and in the same weight ratio as EUD, left both the peak temperature and the enthalpy of fusion per unit P8000C mass virtually unaltered. These findings substantiate hydrogen bonding as the main P8000C-EUD interaction type.

Determining the equilibrium swelling of the semi-IPN in neutral buffer is immaterial, since at neutral pH most of the EUD carboxyls become ionized, the P8000C-EUD complex dissociates and the dissolved EUD diffuses out of the P8000C network during the swelling process. Instead, useful information was obtained from dynamic swelling measurements in neutral buffer. Also, information on the time variation of the complexed and ionized EUD fractions in the

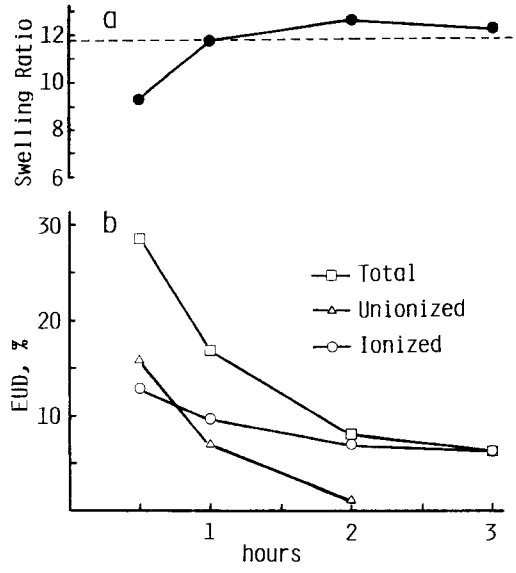

Fig. 2. (a) Dynamic swelling of semi-IPN granules, composed of P8000C/EUD 1:1, in medium I. The dashed line indicates the equilibrium value for pure P8000C. Each data point is the mean of three samples. The range is always within the symbol. (b) Time variation of unionized, ionized and total EUD wt fraction in semi-IPN granules, composed of P8000C/EUD 1:1, during contact with medium I.

semi-IPN during contact with the neutral buffer was obtained by the following procedure. A sample of semi-IPN granules was kept in contact with the buffer for a measured time interval, then it was split into two samples, of which one was dried, the other soaked 4 days in excess water to extract the ionized EUD fraction, then dried. The extracted sample (containing only the unionized EUD) and the non-extracted one (containing both the unionized and ionized EUD) were both equilibrated at 30°C with the acidic solution B (see Table 1), which converted the ionized EUD fraction contained in the non-extracted sample back again into the unionized, interactive form. Each of the equilibrium swollen samples was split into three, the equilibrium swelling ratio was determined for each of the triplicate samples, and the average values for the non-extracted and the extracted samples were used, in conjunction with the swelling-composition curve in Fig. 1, to assess the total (unionized plus ionized) and the unionized EUD fraction contained in the initial sample after

the stated time of contact with the neutral buffer. The ionized fraction was computed by difference.

The above procedure was applied to semi-IPN granules prepared with a 1:1 weight ratio of the component polymers. Samples were kept in contact with a pH 7.4 buffer (solution I, see Table 1) for 0.5, 1, 2 or 3 h at 30°C. The results are shown in Fig. 2b. The data are believed to be sufficiently accurate, since the measurement of the swelling ratio was fairly reproducible and the points of the 'calibration' curve in Fig. 1 are well aligned in the composition range of interest. As shown in Fig. 2a, the semi-IPN attains a swelling value close to the equilibrium swelling value of the pure P8000C after 1 h of contact with the buffer, at which time around 16% EUD (6% unionized, 10% ionized) is still present in the semi-IPN, as Fig. 2b shows. Such a value is not substantially exceeded everafter, since further EUD ionization is accompanied by the exit of the ionized EUD from the P8000C network. In fact, for percentages of EUD in the semi-IPN lower than 30%, the exit rate of the ionized EUD from such a network exceeds the ionization rate of the complexed EUD, as shown in Fig. 2b by the time-decreasing ionized fraction.

3.2. Effect of semi-IPN granules composition on matrix swelling and drug release kinetics

Fig. 3 shows the matrix swelling and drug release rate vs. time profiles for matrices prepared with semi-IPN granules containing varying P8000C/EUD ratios. The granules are medicated with 10% NAM. Fig. 4 shows data for similar matrices containing granules medicated with 10% SAM. Matrix swelling is a consequence of granule swelling, which occurs by means of osmosis (Carelli et al., 1995; Bilia et al., 1996). In accord with the swelling properties of the semi-IPN granules illustrated before, matrices prepared with semi-IPN granules containing higher EUD fractions show lower swelling ratios at even times. An inflection is observed in all matrix swelling profiles of Figs. 3 and 4 in correspondence with the first hour of elution with the pH 6.8 buffer E (see Table 1). Such an acceleration of matrix swelling must be due to the start of EUD ionization in the semi-IPN granules, causing dissociation of the P8000C-EUD complex. Since the silicone elastomer is impermeable to ions, the buffer salts causing EUD ionization must penetrate from matrix surface into granules via intergranule contact surfaces.

Each data point of the release rate vs. time plots in Figs. 3 and 4 represents the drug fraction released in a 1 h interval after time t, and is placed at time $t+0.5$ h. It is observed that, during the elution with SGF, the reduction of matrix swelling ratio caused by an increase of the EUD fraction in the semi-IPN granules is paralleled by a reduction of the drug release rate. Such a correspondence is explained if drug release at this stage is supposed to be controlled by dissolution-diffusion in granules connected to the matrix surface. Indeed, as pointed out in previ-

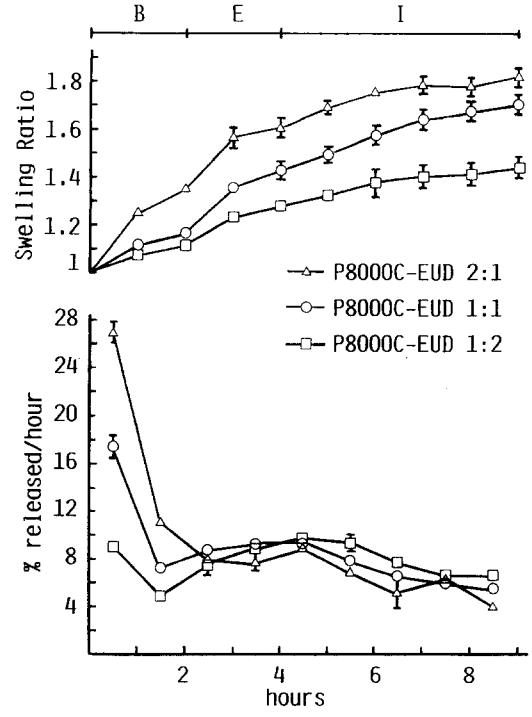

Fig. 3. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate vs. time profiles for matrices prepared with semi-IPN granules of different P8000C/EUD ratios, medicated with 10% NAM. Matrices eluted with media B, E and I, in sequence. Means and S.D. for triplicate runs.

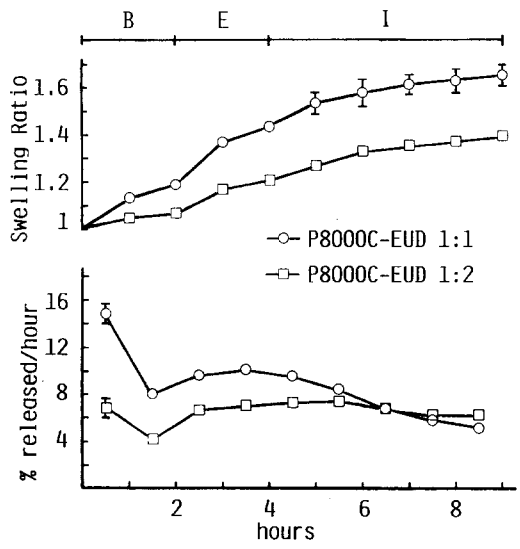

Fig. 4. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate vs. time profiles for matrices prepared with semi-IPN granules of different P8000C/EUD ratios, medicated with 10% SAM. Matrices eluted with media B, E and I, in sequence. Means and S.D. for triplicate runs.

ous reports, a lowering of the granule swelling degree causes a reduction of the granule interconnection degree and, hence, of the granule fraction connected to the matrix surface (Carelli et al., 1995; Bilia et al., 1996). Also, less water in semi-IPN may entail a lower drug diffusivity in granules. In accord with a diffusion-controlled release mechanism, all rate profiles of Figs. 3 and 4 show a descent during the second hour of elution with SGF. The ionization of EUD in the semi-IPN and the consequent dissociation of the P8000C-EUD complex that occur during the successive elution with SIF, must affect the release rate. Indeed, for the matrices prepared with semi-IPN granules containing the P8000C/EUD 1:1 and 1:2 ratios, the rate profile shows an upturn in correspondence with the first hour of elution with SIF, then, after going through a broad maximum, the rate decreases slightly towards the end of the experiment. The process of dissociation of the P8000C-EUD complex must still be incomplete by that time. Indeed, the swelling profiles of Figs. 3 and 4 indicate that none of the matrices has attained its maximum swelling within the time of experiment, and data in Fig. 2 show that some unionized EUD is still present in the P8000C network even at maximum swelling. If drug diffusion in interconnected hydrogel granules is supposed to control the release, then the altogether uniform release rate during elution with SIF can be explained by a progressive increase of drug diffusivity in granules, due to the gradual dissociation of the interpolymer complex and the consequent water uptake, and the continuous formation and/or enlargement of contact surfaces among granules in course of swelling. The rate of drug release to SIF, for the present matrices, is much more uniform in time than that reported previously for similar matrices containing granules made of interpenetrating P8000C and crosslinked poly(acrylic acid) networks (Bilia et al., 1996). With the previous matrices, indeed, the rate peaked sharply at the beginning of elution with SIF, then it rapidly declined. Such a difference is probably due to a response of the previous hydrogel to the change of the environmental pH from acidic to neutral, faster than that of the present semi-IPN.

In Table 2 the cumulative drug dose fractions released in 2 h to SGF, and those released over the whole time of experiment to SGIF are compared for different P8000C/EUD ratios in the semi-IPN. An increasing gastroprotective effect of rising the EUD fraction appears clearly from the data. A comparison between data for NAM and SAM concerning matrix swelling, release rate and cumulative release for corresponding semi-IPN compositions, seen in Figs. 3 and 4 and Table 2, shows no significant differences between the two drugs for the P8000C/EUD 1:1 ratio. Considering the marked differences in solubility between the two drugs, such a similarity of data suggests that both drugs are fully dissolved in granules during release. On the other hand, with the P8000C/EUD 1:2 ratio, matrix swelling, release rate and cumulative release values at corresponding times are lower for SAM compared to NAM, suggesting the presence in granules of some undissolved fraction of the former.

Table 2
Cumulative dose fraction released for matrices prepared with semi-IPN granules of different P8000C/EUD ratios, medicated with 10% drug (means and S.D. for triplicate runs)

Drug	P8000C/EUD in semi-IPN (w/w)	% Load (S.D.) released to SGF in 2 h	% Load (S.D.) released to SGIF in 9 h
NAM	2:1	38.0 (1.1)	85.2 (0.5)
	1:1	24.7 (1.4)	77.9 (3.8)
	1:2	13.9 (0.6)	70.3 (4.2)
SAM	1:1	22.7 (2.2)	78.0 (2.8)
	1:2	10.9 (0.7)	58.7 (1.5)

3.3. Effect of drug dose in semi-IPN granules on matrix swelling and drug release kinetics

Such an effect was studied using matrices prepared with semi-IPN granules containing the P8000C/EUD 1:2 ratio, which has shown the better gastroresistance. Granules were loaded with 5%, 10% or 20% NAM or SAM. The matrix swelling and release rate profiles for the 10% dose are presented in Figs. 3 and 4 for NAM and SAM, respectively, and have already been discussed. Such profiles were not substantially changed by varying the drug load in granules. The cumulative dose fractions released in 2 h to SGF and those released over the whole time of experiment to SGIF for the different doses of the two drugs are compared in Table 3. With the 5% dose, corresponding data show no statistically significant differences between NAM and SAM, probably because, at this dose, both drugs are in the fully dissolved state in the hydrogel granules during release. Increasing the SAM dose to 20% results in a significant decrease ($P < 0.02$) of the dose fraction released in 9 h, probably due to the presence of some undissolved drug fraction in granules during release. Indeed, the inability of semi-IPN granules of the composition being discussed to fully solubilize a 10% dose of SAM in the release course has already been pointed out. On the other hand, corresponding release data for different NAM doses, seen in Table 3, are not significantly different, suggesting that no solid drug fraction was present in granules during release, whichever the dose. Altogether, the data in Table 3 indicate a limited dependence of release on the drug dose, for a given drug, and on the drug type, for a given dose.

3.4. Effects of varying osmolality, ionic strength and buffer molarity of dissolution medium on drug release

These studies were carried out with matrices prepared with semi-IPN granules of P8000C/EUD 1:1 or 1:2 composition, medicated with 10% NAM. The media used are described in Table 1. The osmolality and ionic strength of dissolution medium was increased or decreased with respect to the isotonic media B, E and I by using media C, G and K or A, D and H. The phosphate buffer molarity was decreased by using the sequence B, F and J in place of B, E and I. With every sequence, elution with the first and second medium lasted 2 h, with the third it lasted 5 h. The deviations of matrix swelling and release rate data obtained with the different dissolution media from those presented and discussed before for the elution with the sequence B, E and I were always unnoticeable.

3.5. Characterization of release kinetics

In order to mathematically characterize the release kinetics for the present systems, the following equation:

$$F = kt^n \tag{2}$$

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, was fitted to experimental F vs. t data obtained from matrices prepared with semi-IPN granules containing increasing EUD fractions and medicated with 10% NAM or SAM. As

Table 3
Cumulative dose fraction released for matrices prepared with semi-IPN granules composed of P8000C/EUD 1:2, containing different drug loads

Drug	Drug load in semi-IPN (%)	% Load (S.D.) released to SGF in 2 h	% Load (S.D.) released to SGIF in 9 h
NAM	5	14.5 (1.1)	70.9 (4.8)
	10	13.9 (0.6)	70.3 (4.2)
	20	16.1 (2.0)	77.1 (4.8)
SAM	5	13.1 (1.9)	63.6 (4.6)
	10	10.9 (0.7)	58.7 (1.5)
	20	12.0 (1.0)	48.6 (2.6)

seen in Fig. 5, the fitting is good in all cases. In Table 4, where the regression parameters of Eq. (2) for each semi-IPN composition are listed, it is observed that increasing the EUD proportion causes the rate parameter, k, to decrease and the time exponent, n, to increase, as a result of the increasing control of the release kinetics by the P8000C-EUD complex. With the P8000C/EUD 1:2 ratio, n is close to 1 and the release is of pseudo-zero order for both drugs.

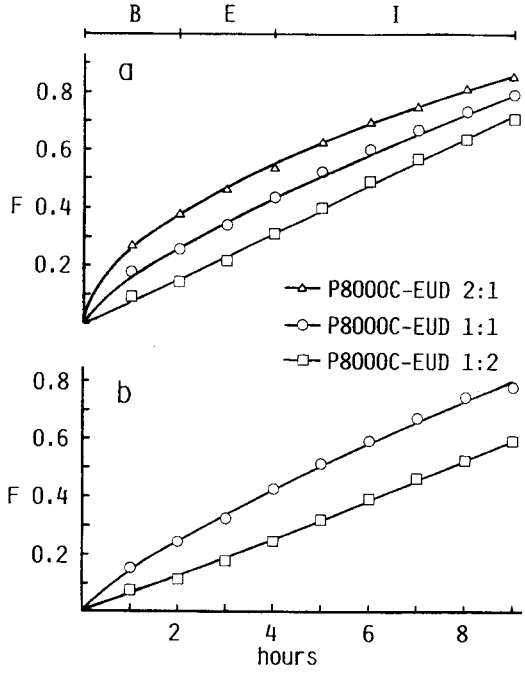

Fig. 5. Fitting of Eq. (2) to release data for matrices prepared with semi-IPN granules of different P8000C/EUD ratios, medicated with 10% NAM (a) or SAM (b). Matrices eluted with media B, E and I, in sequence. Each data point is the mean of three runs.

Considering the importance generally given to constant-rate delivery systems, parameters of Eq. (2) have been determined for matrices prepared with semi-IPN granules containing the P8000C/EUD 1:2 ratio and varying loads of NAM or SAM. They are listed in Table 5. In all cases, the deviation of the exponent n from 1 is within 10%. Also, the variations of the rate constant k with varying load, for a given drug, or drug, for a given load, are limited, considering the range of loads and the difference between the physicochemical properties of the drugs.

4. Conclusions

It has been shown that EUD and P8000C can form an interpolymer complex through hydrogen bonding. The semi-IPN equilibrium swelling in SGF depends inversely on the EUD fraction in the complex. In SIF, the P8000C-EUD complex gradually dissociates, due to the ionization of EUD, which dissolves and diffuses out of the P8000C network. Therefore, the swelling markedly increases in SIF with respect to SGF and gradually attains the value for the pure P8000C. When dispersed in silicone matrices, medicated semi-IPN granules are potentially apt to control the release to the GI tract of drugs having different physicochemical characteristics. Increasing EUD fractions in semi-IPN decrease the release rate in SGF and tend to linearize the overall release profile. A pseudo-zero order release, for either NAM or SAM, has been obtained with matrices prepared with semi-IPN granules containing the P8000C/EUD 1:2 ratio. With this system, the dose fraction released per unit time

Table 4
Regression parameters for the fitting of Eq. (2) to release data for matrices prepared with semi-IPN granules of different P8000C/EUD ratios, medicated with 10% drug

Drug	P8000C/EUD in semi-IPN (w/w)	k (S.E.) (h^{-n})	n (S.E.)
NAM	2:1	0.258 (0.005)	0.55 (0.01)
	1:1	0.155 (0.006)	0.74 (0.02)
	1:2	0.075 (0.005)	1.03 (0.03)
SAM	1:1	0.142 (0.006)	0.79 (0.02)
	1:2	0.057 (0.003)	1.07 (0.02)

Table 5
Regression parameters for the fitting of Eq. (2) to release data for matrices prepared with semi-IPN granules composed of P8000C/EUD 1:2, containing different drug loads

Drug	Drug load in semi-IPN (%)	k (S.E.) (h^{-n})	n (S.E.)
NAM	5	0.079 (0.005)	1.01 (0.03)
	10	0.075 (0.005)	1.03 (0.03)
	20	0.11 (0.01)	0.91 (0.05)
SAM	5	0.058 (0.002)	1.09 (0.00)
	10	0.057 (0.003)	1.07 (0.02)
	20	0.068 (0.002)	0.89 (0.01)

has shown a limited dependence on the dose, in the 5–20% range of drug loads in granules, and, for a given dose, on the drug type, which means that the release is controlled by the polymeric carrier, rather than by the physicochemical properties of the drug. Dose fractions in between 50% and 80% have been released in 9 h from such a system. Drug diffusion in interconnecting semi-IPN granules is the rate-controlling step of the release process. Such a diffusion, in turn, is controlled by the little permeable P8000C-EUD complex and the granule interconnection degree. The tendency of release rate to decrease, typical of a diffusion-governed process, is contrasted by an increase of apparent diffusivity, resulting from both the progressive dissociation of the P8000C-EUD complex and the progressive increase of the granule interconnection degree, the latter due to increasing granule swelling. The release of neither NAM nor SAM is influenced to any important extent by ample variations in osmolality, ionic strength or buffer molarity of the dissolution medium.

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