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In vitro evaluation of a pH-sensitive hydrogel for control of GI drug delivery from silicone-based matrices

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Abstract

The release of drugs having very different aqueous solubilities and partitioning properties, such as salicylamide (SAM), nicotinamide (NAM), clonidine·HCl (CHC) and prednisolone (PDN), from 1 mm thick silicone discs containing, in dispersion, around 35 wt% medicated granules of a pH-sensitive hydrogel, is studied in vitro. The hydrogel is a poly(acrylic acid) (PAA):poly(ethylene oxide) interpenetrating polymer network (IPN). The matrices are eluted with simulated GI fluids, i.e., with a medium of pH 1.2 for 2 h, followed by a medium of pH 6.8 for 2 h, followed by a medium of pH 7.4 for 5 h. The release rate pattern is always bimodal and is determined by the pH-dependent swelling of the IPN granules in matrix. In simulated gastric fluid (SGF) the IPN swelling degree is low and the release is limited to an initial burst, followed by a rapid decline. In simulated intestinal fluid (SIF), PAA in the IPN becomes ionized, the IPN swelling degree increases and the release rate rises to a second maximum. The drug fraction released is always preponderant in SIF compared to SGF. The matrix swelling and drug release rates are influenced by the granule size. With a loading dose of 5 wt% in IPN granules in the 355–425 μm size range, SAM, NAM and PDN show the same release rates in SIF. Differences arise when the load is raised to 20 wt% and/or the granule size range is reduced to 105–250 μm. CHC shows an ionic interaction with PAA in the IPN, which limits the release rate in SIF. The release of drugs not ionically interacting with PAA is virtually uninfluenced by ample variations in osmolality, ionic strength and buffer molarity of dissolution medium.

Keywords: Silicone matrix; pH-sensitive hydrogel; Oral drug delivery system; Clonidine; Prednisolone; Nicotinamide

1. Introduction

In a recent paper by the present authors a composite polymer system was presented, which is able in vitro to release drugs having markedly different aqueous solubilities, such as clonidine·HCl and salicylamide, with the same $\sqrt{t}$-type kinetics and the same release rate per unit drug loading dose (Carelli et al., 1995). Such a system showed a potential for oral use, since it could release around 80% of the loading dose within 6 h to simulated gastrointestinal fluids. It consisted of a disk-shaped, 1 mm thick silicone matrix containing, in dispersion, medicated granules of crosslinked polyethylene glycol 8000

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(P8000-C) able to absorb water up to a 1700 wt% increase. When the system was immersed in the dissolution medium, the P8000-C granules in matrix would swell, connections among granules would gradually 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. With this system 40–45% dose fractions were released to simulated gastric fluid in 2 h. Since the swelling of hydrogel was determinant to the drug release rate, it is reasoned that a hydrogel with a swelling suitably dependent on the pH of dissolution medium, if dispersed in the silicone matrix in place of the pH-insensitive P8000-C, could generate an alternative release pattern, where drug delivery to the intestinal fluid is predominant. In order to realize such a system, an interpenetrating polymer network (IPN) has been used in the present work as the pH-sensitive hydrogel. It consists of P8000-C and poly(acrylic acid) (PAA), which form an interpolymer complex through hydrogen bonding. The stability of the complex is reduced at higher pH values, where most of the PAA carboxyl groups are ionized. This results in reversible swelling or deswelling of the IPN upon increasing or decreasing pH of the external solution (Bednar et al., 1984; Nishi and Kotaka, 1985; Lee, 1991). The IPN has been made into granules of controlled size ranges, the granules have been loaded with drugs covering a wide range of physicochemical properties, such as salicylamide, nicotinamide, prednisolone and clonidine·HCl, and dispersed into silicone elastomer monoliths. The effects of drug type, drug load in granules, granule size range, and composition of dissolution medium on drug release have been studied.

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) and clonidine·HCl (CHC) (Sigma Chemical Co., St. Louis, MO, USA), prednisolone (PDN) (Merck, Darmstadt, Germany), 2-ethyl-2-hydroxymethyl-propane-1,3-diol (EHMPD) (Janssen, Beerse, Belgium).

Tolylene-2,4-diisocyanate (TDIC) (Janssen, Beerse, Belgium) and ethylene glycol dimethacrylate (EGDMA) (Fluka Chemie AG, Buchs, Switzerland) were purified by distillation under reduced pressure before use. Acrylic acid (AA) was distilled under a reduced nitrogen atmosphere of 21 torr just before use. Medical grade polydimethylsiloxane (PDMS) (Silbione RTV 70141, composed of part A and part B) was a gift from Rhône-Poulenc Italia S.p.A., Milano, Italy. Silbione RTV 70141 is a two-component viscous-liquid PDMS which, upon mixing of the two constituents, is transformed into a rubber by room temperature vulcanization. Higher temperatures reduce the vulcanization time.

2.2. Preparation of interpenetrating polymer network (IPN)

Crosslinked PEG 8000 (P8000-C) 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. P8000-C had a 53% crystallinity degree and an equilibrium swelling degree in water at 30°C of 18, expressed as ratio of swollen to dry weights (Carelli et al., 1993). The IPN was prepared from P8000-C according to Nishi and Kotaka (1985). P8000-C was cut into small pieces and swollen with an equimolar amount of AA containing 0.5 wt% AIBN and 1 mol% EGDMA. It took a few minutes for the P8000-C pieces to absorb the AA mixture. The swollen P8000-C mass was placed in a sealed polymerization cell and kept overnight in the dark at room temperature in order for the monomer mixture to become uniformly distributed in the P8000-C network. Then the temperature was raised and kept at 80°C for 48 h to allow polymerization and crosslinking of AA. The product was repeatedly washed with methanol, to remove

Table 1
IPN equilibrium swelling in aqueous media of different pH, osmolality, ionic strength and buffer molarity

Medium	Electrolyte molarity				pH	Osmolality[a] (mOsm kg^{-1})	Ionic strength	IPN swelling strength ratio (SD)[b]
	HCl	Na_2HPO_4	NaH_2PO_4	NaCl				
A	0.04	—	—	0.037	1.5	172	0.077	2.07 (0.06)
B	0.08	—	—	0.074	1.2	306	0.154	1.98 (0.07)
C	0.08	—	—	0.228	1.2	563	0.308	1.89 (0.04)
D	—	0.032	0.033	0.0085	6.9	180	0.137	11.7 (0.5)
E	—	0.064	0.066	0.017	6.8	310	0.275	9.1 (0.3)
F	—	0.016	0.0165	0.12	6.8	308	0.184	9.3 (0.3)
G	—	0.064	0.066	0.171	6.7	588	0.429	8.1 (0.2)
H	—	0.0535	0.0144	—	7.5	165	0.172	10.7 (0.6)
I	—	0.107	0.0228	—	7.4	292	0.344	9.5 (0.4)
J	—	0.0267	0.0057	0.1155	7.5	302	0.201	9.8 (0.5)
K	—	0.107	0.0228	0.154	7.3	572	0.498	8.3 (0.4)

[a]As measured by an osmometer.
[b]Ratio of swollen to dry IPN weights ($n = 5$).

soluble material, until the residue from methanol evaporation was negligible. The dried IPN was a rubbery material and 80 wt% of the initial P8000-C, AA and EGDMA mixture. The formation of the interpolymer complex between P8000-C and PAA was indicated by the absence of the fusion peak of the P8000-C crystallites from the DSC (differential scanning calorimetry) trace of the IPN.

2.3. Measurement of IPN equilibrium swelling

Several pieces of IPN were allowed to swell in the prescribed solvent. Each of five swollen pieces free of internal air bubbles was selected, allowed to attain equilibrium swelling in the solvent at 30°C, as verified by successively blotting and weighing in a weighing bottle, then vacuum dried to constant weight. The swelling degrees in various aqueous solutions of different pH, osmolality, ionic strength and buffer molarity, expressed as mean and standard deviation of the swollen to dry weights ratio, are listed in Table 1.

2.4. Granulation of IPN

Portions of fully water-swollen IPN mass were thrust twice through 250 or 500 μm wire mesh. After drying under a stream of warm air, the granules were sieve-sized to the 105–250 and 355–425 μm ranges. Since the dry granules formed clusters, these were broken by rubbing on the wire meshes.

2.5. Preparation of matrices

The IPN granules were medicated by allowing them to completely absorb a methanolic solution of drug. In order for such a solution to be completely absorbed it should not exceed 250 wt% of dry IPN. The weight and concentration of the solution were designed for a drug load in the dry granules of 5 wt% (cases of SAM, NAM, PDN and CHC) or 20 wt% (cases of SAM and NAM). In order to prevent clustering, the granules were not dried but, rather, they were dispersed in the swollen state in part A of the silicone prepolymer, while stirring under a stream of warm air. When the dispersion was complete and methanol had completely evaporated, the dry granules did not cluster, since they were wetted by the silicone prepolymer. Then, part B of the prepolymer was admixed in the proportion of 10 wt% of part A. The stated proportions of dry medicated granules in the mixture were 25 and 30 wt%, for drug loads in granules of 5 and 20 wt%, respectively. The

dispersion was evenly spread as a thin layer on a glass plate and degassed. Since the development of air bubbles caused some demixing of the dispersion, this was recollected with a spatula and spread again with care to avoid air entrainment. Subsequent degassing left the granule distribution almost unperturbed. Next, the mixture was heated and kept at 50°C for 20 min, during which time the vulcanization of silicone started and the viscosity increased, allowing further handling of the mixture without any major demixing. The mixture was pressed between plastic plates separated by spacers, to obtain 0.1-cm thick sheets from which, after 24-h vulcanization at 50°C, discs of 0.8 cm diameter were cut. All discs were elastic and their surfaces were smooth, non-tacky and hydrophobic. The real weight fractions of medicated granules in matrices, as assessed via determination of the drug content in matrix, were 30.1 ± 1.5 and 33.3 ± 1.2 wt% for the granules in the 105–250-μm size range, loaded with 5 and 20 wt% drug, respectively, and 32.1 ± 1.6 and 36.2 ± 2.2 wt% for the granules of 355–425 μm, loaded with 5 and 20 wt% drug, respectively. Such deviations from the respective nominal values of 25 and 30 wt% were due to some demixing of the granule-prepolymer mixture, which occurred during the matrix fabrication process.

2.6. Kinetic measurements

The matrix was weighed (dry weight), then, at time zero, it was shaken in a known volume of dissolution medium at 37°C. Hourly, the matrix was withdrawn, quickly blotted dry, weighed in a weighing bottle (swollen weight), and immersed in the next fraction of fresh dissolution medium. The drug concentration in each fraction of dissolution medium was determined. Where necessary, before analysis the dissolution medium was cleared of some swollen IPN granules released from matrix, by passing the medium through 105 μm wire mesh. The drug concentration in the receiving phase was never allowed to exceed 2% of solubility, in order to maintain sink conditions. The matrices were eluted for 9 h. If not otherwise indicated, simulated gastrointestinal fluids, consisting of the isotonic media B, E and I, described in Table 1, were used for the elution. The following media were used in the sequence: 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 methanol (PDN) or ethanol-water (1:1) (SAM and NAM), in order to determine the initial drug and granule contents, as stated before. CHC could not be extracted completely by solvents, due to an ionic interaction with the ionized PAA in the IPN, so the initial CHC in matrix was taken as equal to the mean of the values determined for SAM, NAM and PDN, for corresponding drug load in granules and granule size range.

2.7. Statistical methods

The Student's t-test was used to test differences in drug release rate. Differences were considered significant for $p < 0.05$.

2.8. Drug assay

SAM, NAM and PDN were determined spectrophotometrically.

The SAM solutions in ethanol-water (1:1) were read at 299.5 nm, while the aqueous solutions were read at 328 nm, following 1:1 dilution with 0.2 N sodium hydroxide.

The NAM solutions in ethanol-water (1:1) were read at 262 nm, the aqueous solutions at 261 nm.

The methanolic solutions of PDN were read at 242 nm, the aqueous ones at 246.8 nm.

Blank runs always demonstrated the absence of any important interferences with the spectrophotometric assays.

The CHC solutions were analyzed by HPLC, using a Partisil ODS-3 column (C_{18} – 5 μm, 25 cm × 4.6 mm, Whatman, Clifton, NJ, USA) with a mobile phase of acetonitrile-0.01 M phosphate buffer, pH 8 (34:66 v/v), a flow rate of 1.5 ml/min and UV detection at 220 nm.

3. Results and discussion

3.1. Effects of pH, osmolality, ionic stregth and buffer molarity of external medium on IPN equilibrium swelling

As shown in Table 1, the IPN equilibrium swelling ratio is most influenced by whether the pH of the medium is acidic or nearly neutral. Indeed, in accord with previous knowledge (Bednar et al., 1984; Lee, 1991), a change of pH of the external solution from acidic to neutral causes ionization of PAA carboxyl groups in the IPN, resulting in a reduced stability of the PAA-P8000-C complex and, ultimately, in an increased IPN swelling. On the other hand, at even pH, changes in osmolality, ionic strength, and/or buffer molarity of the external medium produce only limited effects on the IPN swelling ratio. Specifically, at nearly neutral pH, when the osmolality of the medium is increased by a factor of around 2, or decreased by a factor of around 0.55 with respect to the isotonic value, the swelling ratio decreases only by a factor of around 0.9, or increases only by a factor of around 1.2 (compare data for media D, E and G, or H, I and K). At even pH and osmolality, a reduction of phosphate buffer molarity by a factor of 0.25 and the consequent reduction of ionic strength by a factor of around 0.6 produces no significant effect on the swelling ratio (compare data for media E and F, or I and J).

3.2. Matrix swelling and drug release for matrices prepared with IPN granules of 355–425 μm

Fig. 1 represents the matrix swelling and release rate profiles for matrices containing IPN granules medicated with 5 wt% SAM or NAM. In accord with the data on IPN swelling, shown in Table 1, both profiles of matrix swelling ratio show essentially two levels, the lower one corresponding to matrix contact with the acidic medium B, the higher one due to ionization of PAA in the IPN, following matrix contact with the nearly neutral buffers, E and I. Although the matrix swelling ratio measured in media E and I appears from Fig. 1 to be virtually constant in time for both matrices, it cannot be said whether or not the IPN in matrix has reached swelling equilibrium. Indeed, the value of the matrix swelling ratio is negatively affected by the release of drug and the loss of IPN granules from matrix, in fact, a number of granules were seen to have left the matrix during elution with media E and I. Nevertheless, the jump of swelling ratio corresponding with the first hour of elution with medium E, apparent in both swelling profiles of Fig. 1, leaves little doubt that the IPN in matrix experiences its maximum swelling rate during such a time.

Each data point of the release rate vs. time plots represents the drug fraction released in a 1 h interval after time t, and is placed at time $t + 0.5$ h. The release rate profiles, shown in Fig. 1, are both bimodal. The first rate maximum is at the beginning of elution with the acidic medium B. Drug release at this stage is presumably controlled by dissolution-diffusion from IPN granules in contact with the matrix surface, and also by partitioning to and diffusion through the silicone elastomer. The replacement of medium B by medium E, used to mimic the fluid of the upper small intestine, starts the second stage of release, where the rate rises to a second maximum, significantly higher than the first one, and then tapers off. It clearly appears from Fig. 1 that the release accel-

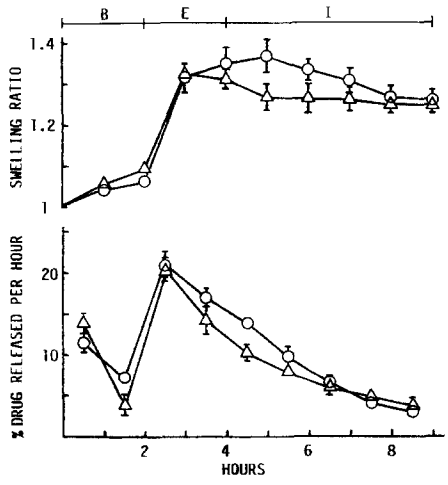

Fig. 1. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate versus time profiles for matrices containing IPN granules of 355–425 μm, treated with 5 wt% SAM (○) or NAM (△). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

erates most in coincidence with the maximum swelling rate of matrix. This suggests that, at this point, the release of both drugs mainly occurs by diffusion through interconnected IPN granules and is controlled by the formation and/or enlargement of connections among swelling granules, which increases the IPN mass fraction connected to the matrix surface. As the swelling rate decreases in time, drug diffusion in the swollen interconnected hydrogel would take control of the release process, and this would explain the tapering off of release rate. The release rate data for SAM and NAM, shown in Fig. 1, are altogether similar, despite the large difference in aqueous solubility between the two drugs (1 g/500 ml vs. 1 g/1.5 ml, according to Remington's Pharmaceutical Sciences, 1980). This suggests that both drugs are fully dissolved in the swollen IPN. Also, drug partitioning to silicone and drug molecular interactions with the IPN, which should be sources of differences in release rate between the two drugs, must altogether be of limited relevance to release.

When the drug load in the IPN granules is raised to 20 wt%, the differences in matrix swelling and drug release between the SAM and NAM matrices become significant, as Fig. 2 shows. At this load, the highly hydrophilic NAM exerts a significant osmotic activity which adds to that of the IPN and results in a peak in the matrix swelling profile, followed by a descent due to the release of the osmotically active drug from matrix. The drug promotes its own release via the hydrogel by means of osmosis, and this leads to a faster release with respect to the cases discussed before. The results from a comparison between the release rate data in Figs. 1 and 2, concerning the two different loads of SAM, differ significantly only in one point, corresponding to the maximum matrix swelling rate. Here, the fractional release rate for the 5 wt% load is higher than that for the 20 wt% load, presumably because in the former instance the drug is fully dissolved in the hydrogel, whereas in the latter a portion of drug is still in the dispersed state.

The behavior of matrices containing IPN granules medicated with 5 wt% PDN or CHC, illustrated in Fig. 3, is altogether similar to that seen in Fig. 1 for the SAM and NAM matrices. The

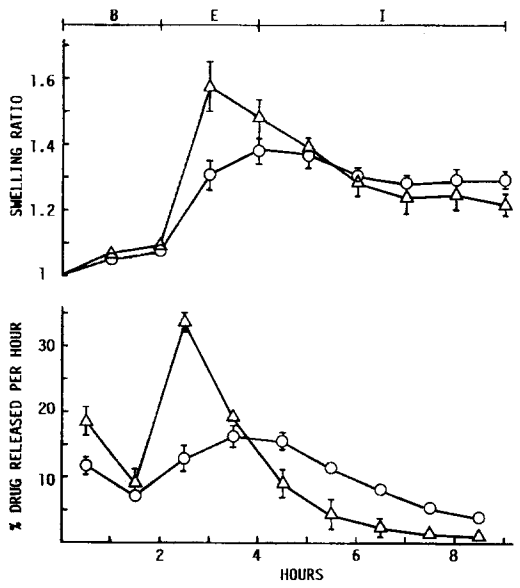

Fig. 2. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate versus time profiles for matrices containing IPN granules of 355–425 μm, treated with 20 wt% SAM (○) or NAM (△). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

similarity of release rate profiles suggests that with PDN or CHC, as well as with SAM or NAM, drug dissolution-diffusion in the interconnected IPN phase is the prevailing release mechanism. In fact, previous reports have shown that partitioning and diffusion in the silicone elastomer gives little contribution to the release of either PDN or CHC from porous silicone matrices (Di Colo et al., 1986; Carelli et al., 1987).

From a comparison of the release rate maxima for the 5 wt% load in granules, listed in Table 2, the first maximum for PDN appears to be significantly lower than the corresponding maxima for SAM, NAM and CHC, which are not significantly different from one another. This may be ascribed to a lower solubility of PDN in the IPN at the un-ionized swelling level. On the other hand, the second rate maximum for PDN is indistinguishable from the corresponding maxima for SAM and NAM, suggesting that PDN, as well as SAM and NAM, is fully dissolved in and non-interacting with the IPN at the ionized swelling level. The second rate maximum for CHC is

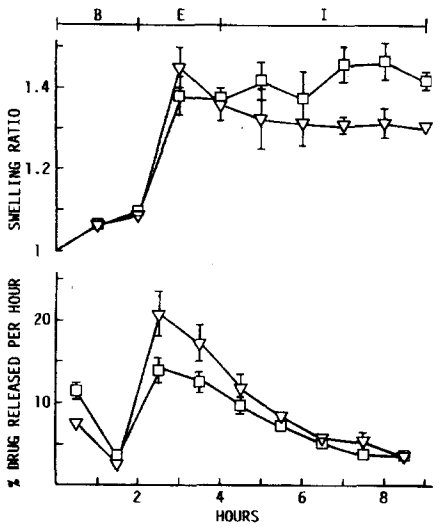

Fig. 3. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate versus time profiles for matrices containing IPN granules of 355–425 μm treated with 5 wt% PDN (▽) or CHC (□). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

significantly lower than the corresponding maxima for SAM, NAM and PDN. This is ascribable to an interaction of the cationic drug with the anionic PAA in the IPN, in its ionized form. Such an interaction should be absent during elution with the acidic medium B, when PAA is in the un-ionized form and interpolymer complexation prevails. An ionic interaction between the positively charged propanolol and the negatively charged poly(methacrylic acid) in a poly(ethylene oxide)-poly(methacrylic acid) IPN has already been reported (Lee, 1991).

The cumulative drug fraction released to simulated gastrointestinal fluids (media B, E and I in sequence) in 9 h and that released to simulated gastric fluid (medium B) in 2 h for the matrices discussed so far are listed in Table 2. In all cases, the dose fraction released to the gastric fluid is limited. The highest value refers to the case of NAM, loaded at the 20 wt% level, where the drug facilitates its own release by means of its osmotic activity, the lowest corresponds to PDN and is due to the low solubility of this drug. The dose fraction released to the gastrointestinal fluids in 9 h is generally high. The lowest value refers to CHC and is due to the ionic interaction of this drug with PAA in the IPN.

3.3. Matrix swelling and drug release for matrices prepared with IPN granules of 105–250 μm

In the previous paper (Carelli et al., 1995) a reduction of size of hydrogel granules dispersed in silicone matrices was shown to result in a reduced ability of granules to create and/or enlarge intergranule connections by means of swelling. This is probably the reason why a decrease of size of IPN granules from 355–425 to 105–250 μm causes major changes in both swelling and release behavior of the present matrices. It appears from a comparison of the swelling profiles for the matrices containing the smaller granules, represented in Figs. 4–6, with those of Figs. 1–3, relative to the larger granules, that in the former instance matrix swelling is much slower and gradual than

Table 2
Drug release data for matrices prepared with IPN granules in the 355-425 μm size range (means and SD for triplicate runs)

Drug	Drug load in IPN (wt%)	Rate maximum (SD) (% load h^{-1})		% load (SD) released to	
		1st	2nd	Medium B, in 2 h	Media B, E and I, in 9 h
SAM	5	11.5 (1.2)	20.9 (1.6)	18.0 (0.6)	91.5 (1.4)
	20	11.8 (1.0)	16.2 (1.7)	19.0 (0.6)	90.2 (2.0)
NAM	5	13.9 (1.1)	20.3 (1.3)	17.6 (2.4)	85.9 (1.9)
	20	18.4 (2.2)	33.6 (1.1)	27.7 (4.1)	98.5 (1.1)
PDN	5	7.5 (0.5)	20.8 (2.6)	10.1 (0.5)	83.6 (6.1)
CHC	5	11.6 (1.0)	14.1 (1.4)	15.3 (1.2)	72.6 (5.6)

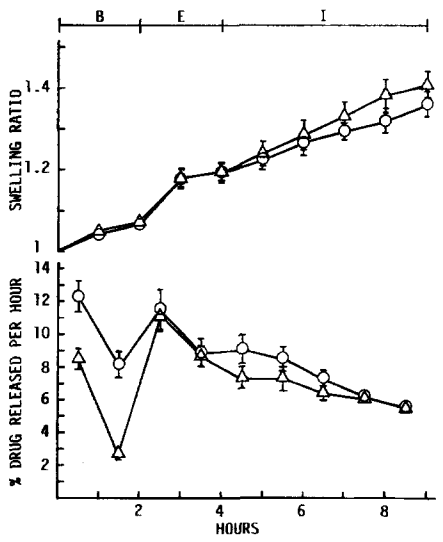

Fig. 4. Matrix swelling ratio (ratio of swollen to initial dry matrix weigths) and fractional drug release rate versus time profiles for matrices containing IPN granules of 105–250 μm, treated with 5 wt% SAM (○) or NAM (△). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

in the latter. Since the silicone polymer is impermeable to the buffer salts, these are supposed to penetrate into the IPN granules via diffusion through the intergranule connections. Therefore, if more restricted connections among the smaller granules are admitted, then the slower matrix swelling with such granules can be explained by a slower salt diffusion and PAA ionization.

The release rate profiles, shown in Figs. 4–6, are bimodal as in the cases of the larger granules discussed before. Except for the case of SAM, the first rate maximum as well as the drug fraction released to medium B, shown in Table 3, are always lower than in the corresponding cases in Table 2, concerning the larger granules. This is consistent with the hypothesis made before that the release at this point essentially occurs via dissolution-diffusion from IPN granules in contact with the matrix surface. Indeed, with smaller granules the IPN mass fraction in contact with the surface should be smaller than with the larger ones (Kaewvichit and Tucker, 1994). In the case of SAM, drug partitioning and diffusion in silicone could be, in the first stage of release, of relevance sufficient to mask the effect of the decreased granule size. As in the cases of the larger granules discussed before, the second rate maximum is always associated with a jump in the swelling profile, corresponding with the replacement of the acidic medium B by the nearly neutral buffer E, although such a jump and associated rate maximum are always lower than in the corresponding cases with the larger granules (compare Figs. 4–6 with Figs. 1–3). Once again this is consistent with a release mainly controlled by diffusion through intergranule connections. Indeed, with the smaller granules the rate at which such connections are formed and/or enlarged by granule swelling is lower, and so is the release rate. The similarities or differences among the rate maxima in simulated intestinal fluid for SAM, NAM and CHC, seen in Table 3, are virtually the same as those noticed in Table 2 for the matrices prepared with granules of 355–425 μm, therefore the considerations made before concerning the physical state of these drugs in the IPN, the effects

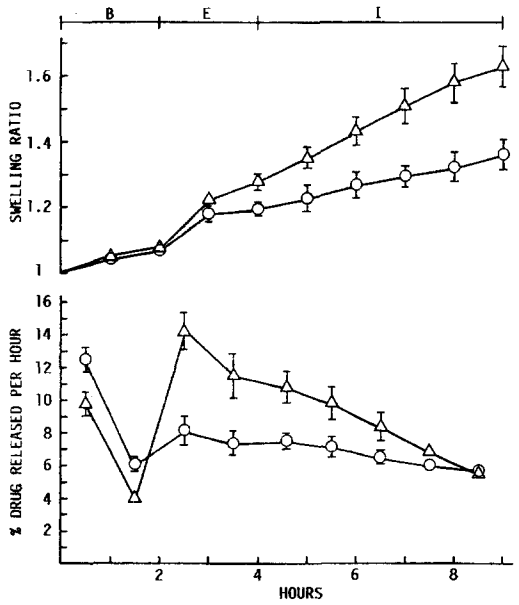

Fig. 5. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate versus time profiles for matrices containing IPN granules of 105–250 μm, treated with 20 wt% SAM (○) or NAM (△). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

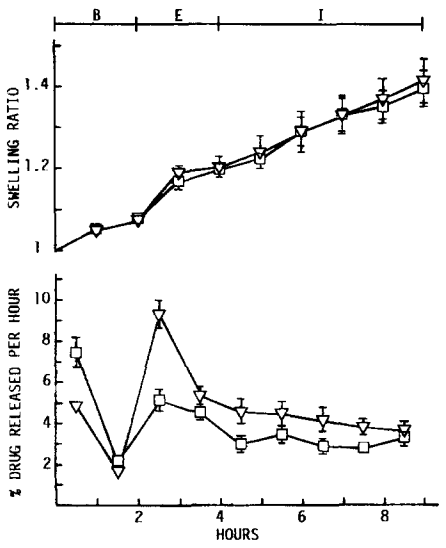

Fig. 6. Matrix swelling ratio (ratio of swollen to initial dry matrix weights) and fractional drug release rate versus time profiles for matrices containing IPN granules of 105–250 μm, treated with 5 wt% PDN (▽) or CHC (□). Matrices eluted with media B, E and I, in sequence. Means and SD for triplicate runs.

on release of increasing the load of SAM and NAM from 5 to 20 wt%, and the ionic interaction of CHC in the IPN, also apply to the matrices prepared with granules of 105–250 μm. On the other hand, the release rates for PDN, reported in Fig. 6, are significantly lower than those for SAM and NAM, seen in Fig. 4, unlike the case of the larger granules, where the rates for SAM, NAM and PDN in the intestinal stage of release, reported in Figs. 1 and 3, are similar. This suggests that with the smaller granules the low solubility of PDN is part of the rate-limiting factors in both stages of release.

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 IPN granules in the 105–250 or 355–425 μm size range, loaded with 5 wt% SAM. 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.

4. Conclusions

With all the different drug types tested, release is largely controlled by the pH-dependent swelling of the IPN granules in matrix. In simulated gastric fluid the PAA in the IPN is un-ionized and the matrix swelling degree is very low. In these conditions the release is limited to an initial burst, followed by a rapid decline, and is controlled by drug dissolution-diffusion from IPN granules in contact with the matrix surface and, secondarily, by drug partitioning and diffusion in the silicone elastomer. When the gastric fluid is replaced by intestinal fluid, the PAA in the IPN tends to become ionized, the matrix swelling rate accelerates and the release rate rises to a second maximum. In this phase, the release is mainly controlled by the formation and/or enlargement of interconnections among IPN granules, consequent to granule swelling. Subsequently, the matrix swelling rate decreases and so does the release rate, which gradually tends to be determined by drug diffusion or dissolution-diffusion in the interconnected swollen granules. The matrix swelling and drug release rates are influenced by the granule size, since this determines the size of the intergranule connections through which the drug is released and the buffer salts diffuse into the granules to produce PAA ionization and IPN swelling. With all the different drug types tested, the drug fraction released during the simulated gastrointestinal transit of matrix is preponderant in the intestinal compared to the gastric fluid. With a loading dose of 5 wt% in IPN granules in

Table 3
Drug release data for matrices prepared with IPN granules in the 105–250-μm size range (means and SD for triplicate runs)

Drug	Drug load in IPN (wt%)	Rate maximum (SD), (% load h^{-1})		% load (SD) released to	
		1st	2nd	Medium B, in 2h	Media B, E and I, in 9 h
SAM	5	12.3 (0.9)	11.5 (1.1)	20.4 (1.7)	77.5 (6.4)
	20	12.5 (0.7)	8.1 (0.9)	18.5 (1.2)	66.9 (4.8)
NAM	5	8.5 (0.7)	11.1 (0.7)	11.3 (0.9)	63.8 (4.4)
	20	9.7 (0.7)	14.2 (1.1)	13.7 (0.4)	81.0 (5.2)
PDN	5	4.9 (0.1)	9.3 (0.6)	6.6 (0.2)	42.2 (3.8)
CHC	5	9.4 (0.8)	5.2 (0.5)	9.8 (0.6)	35.3 (1.8)

the 355–425 μm size range, drugs having very different aqueous solubilities and partitioning properties, such as SAM, NAM and PDN, show much the same release rates in the intestinal stage of release. However, differences arise when the load is raised to 20 wt% and/or the granule size is reduced to 105–250 μm. The cationic CHC shows a significant interaction with the ionized PAA in the IPN, which limits the release rate of this drug in the intestinal fluid. The release of drugs not ionically interacting with PAA in the IPN is not influenced to any important extent by ample variations in osmolality, ionic strength and buffer molarity of the dissolution medium.

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