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Factors in zero-order release of clonidine hydrochloride from monolithic polydimethylsiloxane matrices

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Summary

Clonidine hydrochloride loading doses in the 20–40% range are released from monolithic polydimethylsiloxane (PDS) matrices through a self-triggered osmotic pumping mechanism via cracks having formed in the stressed polymer. This mechanism results in zero-order release kinetics when drug particles in the 50–150 μm size range and filler-reinforced PDS are used. Changes in matrix shape (disk vs cylinder) are inconsequential to the zero-order pattern, whereas they do affect release rate. A strong influence of drug loading dose on this rate, as quantified by a highly significant log–log correlation, allows the rate to be modulated over a wide range of pharmacologically interesting values. The zero-order regimen, which lasts several days or months depending on matrix shape and drug load, is preceded by a burst effect and followed by a decline of rate when osmotic pumping ends and the matrix starts shrinking. By this time, around 50% of initial drug load has been released. Release rate is also affected by the pH and buffering competence of the receptor medium.

Introduction

In a previous report a novel use of polydimethylsiloxane (PDS) for design of monolithic matrices ensuring long-term administration of osmotically active drugs at constant rate was anticipated (Di Colo et al., 1984). Matrices loaded with sodium salicylate or lidocaine hydrochloride were shown to first rapidly swell to attain osmotic equilibrium with the elution medium, and then slowly shrink at a constant rate thereby releasing drug at zero-order. The release rates were so low as to point to this model system as a potential tool for multi-month subcutaneous administration of highly bioactive osmotic agents. However, as recent work with PDS matrices has demonstrated, the osmotic activity of either the therapeutic agent or other dispersed water carriers may lead to very different physical features of the release system depending on osmotic power and dispersion degree of water carriers, polymer plasticizing effects of ingredients, concentration and dispersion degree of solids in matrix (Carelli and Di Colo, 1983; Carelli et al., 1986; Di Colo et al., 1984; Di Colo et al., 1986; Hsieh et al., 1985; Hsieh and Chien, 1985). Therefore, extension of the zero-order model to drug-salts with very different osmotic competence is not expected to be straightforward.

The aim of this work was to investigate the

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range of conditions, such as drug loading dose, drug particle size, and matrix shape, under which monolithic matrices based on medical grade PDS could possibly release clonidine hydrochloride, an interesting candidate of which oral and transdermal sustained release dosage formulations have already been developed, at constant, pharmacologically interesting rates.

Materials and Methods

Materials

Clonidine hydrochloride (Sigma, St. Louis, MO, U.S.A.), polydimethylsiloxane elastomer and silica filler (PDS) (Silastic 382 medical grade elastomer, Dow Corning, Midland, MI, U.S.A.), fillerless PDS (Silastic 382 medical grade elastomer, fillerless, gift from Dow Corning, Midland, MI, U.S.A.) and stannous octoate (Catalyst M, Dow Corning, Midland, MI, U.S.A.) were used as received, each from a single batch. For some experiments, fine crystals of clonidine hydrochloride were prepared through precipitation from a vigorously stirred 20% w/v methanolic solution with excess ethyl ether at room temperature.

PDS sheetings of 5 mil labeled thickness (Silastic, Dow Corning, Midland, MI, U.S.A.) were used as membrane material.

Particle size analysis

Particle size analysis of drug powder was carried out with a Reichert-Jung Microstar 120 projection microscope (American Optical, Buffalo, NY, U.S.A.) following the procedure recommended by Speiser (1967). With each powder more than 700 particles were classified according to their projected diameter, and the volume frequency distribution was calculated. The re-crystallized powder was in the 50 μm size range, with a mean volume diameter of 30 μm and a 98% volume fraction in the 10–50 μm range. The commercial product was in the 150 μm size range, with a mean volume diameter of 90 μm and a 92% volume fraction in the 50–150 μm range.

Preparation of matrices

The drug powder was homogeneously dispersed into the prepolymer; after admixture of 0.5% stannous octoate catalyst the mixture was pressed into sheets of 0.05 cm or 0.1 cm thickness, or added to a plastic mold to form cylindrical pellets of 0.6 cm diameter and 0.3 cm height, then allowed to cure overnight at room temperature. Disks of 1 cm diameter were cut from the vulcanized sheets. Matrices were always prepared from filler-reinforced PDS and commercial drug powder, except in some specified instances where fillerless PDS or re-crystallized drug was used. The weights of the 0.05-cm and 0.1-cm thick disks were in the 47–53 mg and 96–100 mg ranges, respectively. The pellets ranged between 100 mg and 110 mg. All matrices were apparently elastic. Their surfaces were visually smooth and hydrophobic.

Kinetic measurements

The procedure for determination of drug release and matrix swelling kinetics was the same as that reported previously (Di Colo et al., 1982). Matrices were shaken in isotonic phosphate buffer (0.13 N, pH 7.4) or normal saline at 37°C. The drug concentration in the receptor medium was determined by making samples to pH 13 with 1 N sodium hydroxide and spectrophotometrically analyzing at 240 nm. At this wavelength the UV spectrum of the alcalinized samples exhibited a shoulder with absorbance proportional to drug concentration, at least within the 5–50 μg/ml range. Where the plot of cumulative amount of drug released versus time showed apparently linear portions, these were separately analyzed by linear regression. Analysis was extended to data points in the portion of plot that gave the best fit. All regressions were highly significant ($P < 0.001$). Each of the reported release rates resulted from the averaged slopes for at least 3 runs carried out with distinct batches of identical formula.

Solubility determinations

The solubility of clonidine hydrochloride in water or in either receptor medium used for the kinetic experiments was determined by equilibrating excess of drug with solvent at 37°C, then rapidly filtering through a 0.45 μm pore size polytetrafluoroethylene filter (SM 11806 Sartorius GmbH, Gottingen, F.R.G.) and spectrophotomet-

rically analyzing the clear solution for the drug, after dilution and alcalinization, as described in the preceding paragraph. The results listed in Table 1 show little differences between solubilities in the various solvents.

Permeation measurements

The flux of clonidine hydrochloride through a PDS membrane (7.55 cm^2 surface area; 145 μm thickness, as determined by a micrometer) at 37°C was measured using similar diffusion cell and apparatus as those described by Bottari et al. (1975). The thermodynamic activity of the drug at the donor side of the membrane was kept constant by applying a stirred suspension of drug in water. Sink conditions at the receptor side were ensured by a stirred isotonic sodium chloride solution which was analyzed daily for the drug and then renewed. The difference in osmotic pressure between donor and receptor phases caused a slow increase of donor phase volume throughout the experiment, corresponding to less than a 2% daily decrease of external phase volume. At the end of the experiment, solid drug particles were still visible in the donor phase. The plot of cumulative amount permeated per unit membrane surface versus time, shown in Fig. 1, is clearly linear ($r = 0.9993$), indicating a time-constant permeability of clonidine hydrochloride through PDS in the presence of a water counterflow. The value for the permeability, as calculated from the following equation:

$$\text{permeability} = \frac{(\text{permeant flux})(\text{membrane thickness})}{(\text{water solubility of permeant})}$$

TABLE 1

Solubility data for clonidine hydrochloride at 37°C

Solvent	Solubility (mg/ml)
Water	92.7
Buffer	101.0
Saline	90.7

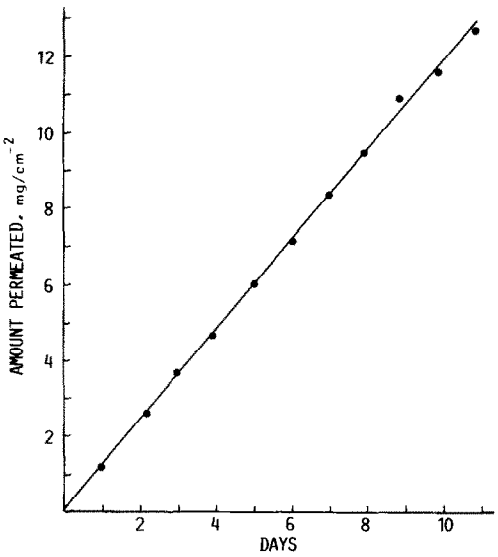

Fig. 1. Plot of permeation data (see text).

assuming Fickian diffusion in membrane, was $2.14 \cdot 10^{-9}\ cm^2 \cdot s^{-1}$.

Partition coefficient determination

Three grams of PDS membrane material were cut into small pieces, then brought into intimate contact with 3 ml of a 5% w/w water solution of clonidine hydrochloride, removing entrapped air bubbles by suction. Equilibration at 37°C, which was monitored by periodically analyzing 50 μl samples of solution, took about 13 days. The equilibrium w/w drug concentration in PDS was calculated from the solution depletion. The value for the PDS–water partition coefficient, expressed as ratio of w/w concentrations, was 0.086.

Results and Discussion

Representative data on drug release to the buffer and relative matrix swelling for 0.05-cm and 0.1-cm thick disks loaded with 20% drug are presented in Figs. 2 and 3, respectively, along with plots of mean drug concentration in matrix fluid (Cmf) versus time. Each Cmf value was calculated as ratio of drug weight remaining in matrix to the difference between weight of swollen matrix and

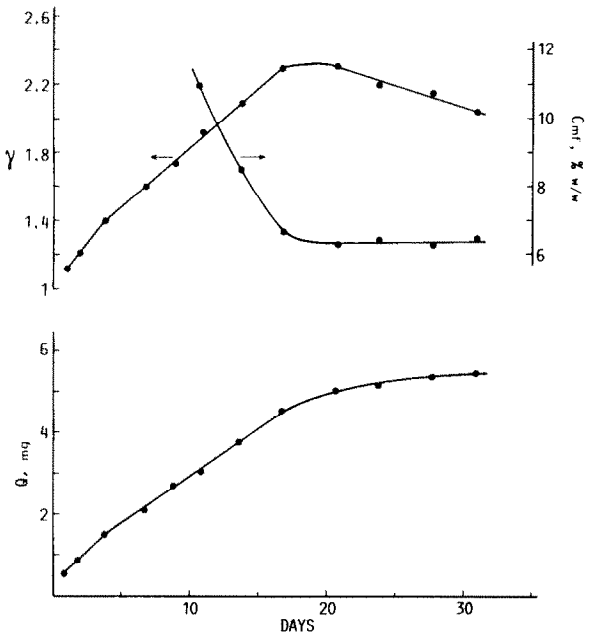

Fig. 2. Plots of representative data on 20% clonidine hydrochloride release (Q, cumulative amount released) from PDS disks (0.05 cm thick) to phosphate buffer pH 7.4, and corresponding matrix swelling (γ, ratio of swollen-to-dry matrix weights). Calculated values of mean drug concentration in matrix fluid (Cmf) are also plotted versus time.

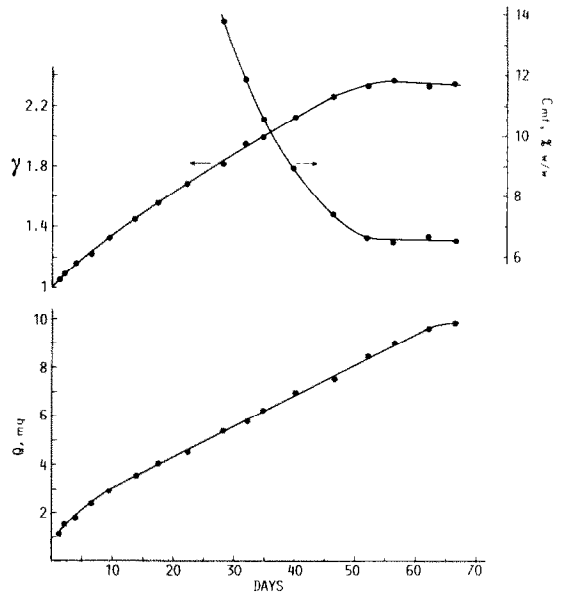

Fig. 3. Plots of representative data on 20% clonidine hydrochloride release (Q, cumulative amount released) from PDS disks (0.1 cm thick) to phosphate buffer pH 7.4, and corresponding matrix swelling (γ, ratio of swollen-to-dry matrix weights). Calculated values of mean drug concentration in matrix fluid (Cmf) are also plotted versus time.

weight of PDS (plus catalyst) formulated within matrix, assuming that a progressive hydration of the interspersed drug particles by osmosis was the only cause of solvent uptake into matrix and the whole drug in matrix was either suspended or dissolved in the resulting aqueous cells. This assumption is elicited by the rather low value determined for the polymer–water partition coefficient of the drug (see Materials and Methods). As can be seen in Figs. 2 and 3, constant Cmf values and maximum swelling were attained simultaneously. With previously studied osmotic matrices employing sodium salicylate or lidocaine hydrochloride as the agents the attainment of a similar equilibrium marked the starting point of a zero-order release kinetics (Di Colo et al., 1984). The present pattern, however, must be quite a different one, since an apparent zero-order regimen sets in shortly after the start of matrix swelling and lasts until maximum swelling is attained; then the rate tails off significantly. These differences go along with a longer-lasting swelling stage and a flatter swelling curve compared to the previous devices. Such a swelling behavior of the present ones may be due to a comparatively low water solubility of clonidine hydrochloride limiting the osmotic activity of this agent. Indeed, a comparison of the Cmf values appearing in Figs. 2 and 3 with the solubility values given in Table 1 suggests that the mean drug concentration in matrix fluid should be above solubility over almost the whole swelling stage, which was clearly not the case with the previous matrices.

Doubling the disk thickness (0.1 cm vs 0.05 cm) nearly halved the zero-order release rate, as appears in Table 2 from the Rs values relative to the disks. Such a thickness effect on the steady rate is hardly explained unless it is linked to the lower swelling degrees and/or swelling rates of the thicker disk at even time points in the stationary stage, appearing from a comparison of the respective plots in Figs. 2 and 3. This could be an

TABLE 2

Stationary release rates (Rs) for matrices having different shapes and drug loads

Shape	Load (%)	Elution medium	Rs (S.D.) (μg/day)
Disk (0.05 cm thick)	20	buffer	218 (17)
Disk (0.1 cm thick)	20	buffer	128 (6)
Cylinder	20	buffer	53 (2)
	20	saline	74 (1)
	25	buffer	98 (5)
	25	saline	130 (4)
	30	buffer	177 (14)
	30	saline	232 (5)
	40	buffer	403 (15)
	40	saline	522 (20)

explanation if both a dependence of the release rate on solvent uptake and the absence of penetrating solvent (or swelling) fronts in matrix in the stationary-rate stage are admitted. Solvent fronts, indeed, must have met early in the release course, otherwise a semi-infinite model with thickness-independent release rate would have been operative. Some swelling gradients, nevertheless, clearly appeared in the swelling stage from a deformation of the disk shape which tended to disappear on approaching maximum swelling. Since the polymeric walls of the aqueous cells generated by solvent uptake should be opposing a rate-determining resistance to drug flux an action of the cell fluid to progressively increase the perviousness of such walls is expected to be the effect of solvent uptake most relevant to drug release. Such an effect could not have resulted from molecular interactions of either or both water and drug with polymer, since drug partitioning into and permeability through an unstressed PDS membrane were shown in the experimental section of this report to be both poor and time constant. Most likely, then, the action of solvent on matrix material was essentially mechanical in nature. Discussion of this point will be resumed later on, on the basis of further evidence.

Effects of matrix shape and receptor medium

Cylinders of 0.6 cm diameter, 0.3 cm height and same weight as the 0.1-cm thick disks were made up to investigate matrix shape and receptor medium effects on the release pattern. Data in Fig. 4 show that the cylinders also released drug at a constant rate. Either swelling or release data obtained eluting matrices from the same batch with isotonic receptor media of different composition, namely, normal saline or pH 7.4 phosphate buffer, were insensitive to the medium at the early times, then, in the stationary-rate period the release rate with the former medium became higher and the swelling values lower than with the latter. Differences of a similar magnitude were observed with replicate batches. Oddly, solvent penetration into matrix was apparently restrained in the case of faster release, as results from the mean drug concentration in the cell fluid being the higher in this case at any time point in the stationary-rate

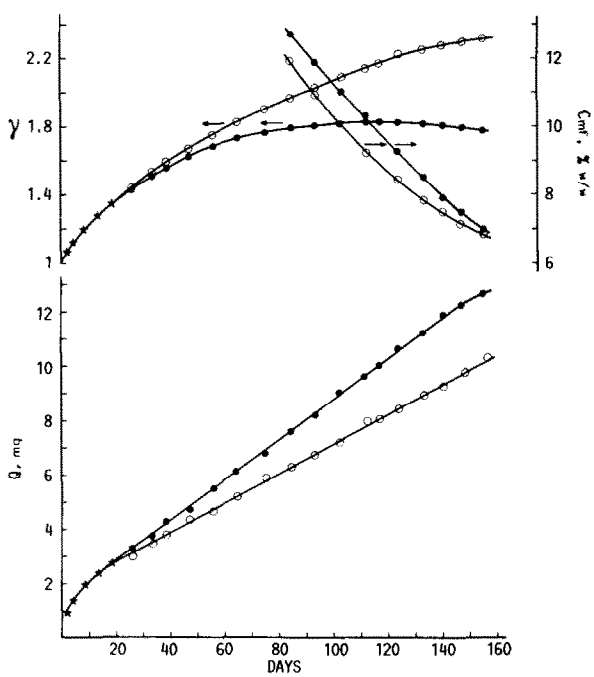

Fig. 4. Plots of representative data on 20% clonidine hydrochloride release (Q, cumulative amount released) from cylindrical PDS pellets to two different media, and corresponding matrix swelling (γ, ratio of swollen-to-dry matrix weights). For each case calculated values of mean drug concentration in matrix fluid (Cmf) are also plotted versus time. Key: ○, phosphate buffer pH 7.4 as receptor medium; ●, normal saline as receptor medium; ★, superimposed points. Matrices were from the same batch.

period. These findings can be best understood if an efflux of matrix fluid from the start of this period is admitted and the swelling degree at each time point regarded as the net result of simultaneous inward flux of solvent and outward flux of drug solution. The latter flux might be driven by a sort of osmotic pumping mechanism through microcracks having formed in the polymer continuum in response to the solvent-induced stress. The slower release with the buffered medium may then be ascribed to an action of phosphate ions penetrating from medium into the cell fluid to hinder the development of such cracks, possibly through an influence on the pH of this fluid which could, in turn, affect the strength of physical bonds in the polymer network. The drug solubility in the cell fluid, on the other hand, could little be affected by ions from the receptor medium, as data in Table 1 clearly show. In order to bring the effect of cracks into clearer evidence disks of same size and drug load as those referred to in Fig. 2 were made up with fillerless silicone elastomer. Also, the effect of receptor medium on these matrices was studied using samples from a single batch. Data plotted in Fig. 5 show no dramatic differences in swelling behavior with respect to the reinforced disks of Fig. 2. The release curve, nonetheless, exhibits an upward bending in the swelling stage which can safely be attributed to progressive cracking. The filler then seems to be one rate-controlling factor insofar as it limits the propagation of cracks. Some differences in release rate between the two receptor media are still observed in the absence of filler, even though their magnitude is considerably reduced.

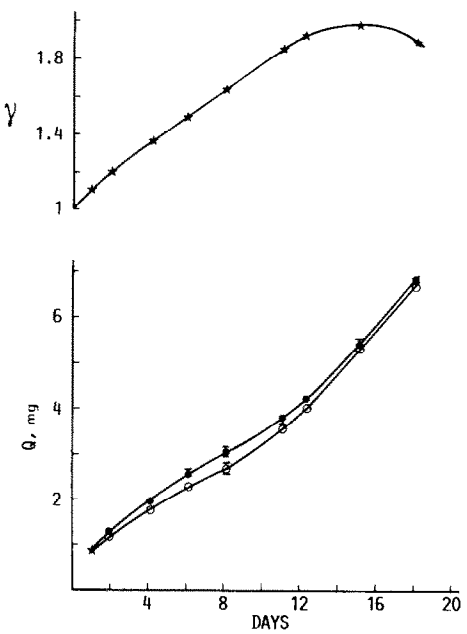

Fig. 5. Plots of data on 20% clonidine hydrochloride release (Q, cumulative amount released) from fillerless PDS disks (0.05 cm thick) to two different media, and corresponding matrix swelling (γ, ratio of swollen-to-dry matrix weights). Key: ○, phosphate buffer pH 7.4 as receptor medium; ●, normal saline as receptor medium; ★, superimposed points. Data points are averaged values from triplicate runs. Bars represent the ranges. Where not shown they fall within the drawn symbol. All matrices were from the same batch.

Effect of drug load

The release and swelling patterns for cylinders loaded with 25%, 30% or 40% drug and eluted with either buffer or saline are typified in Fig. 6. Mean zero-order rates are listed in Table 2. Such patterns suggest that the release mechanism is unmodified by changes in drug load over the 20–40% range. The release rate, on the other hand, is exceedingly sensitive to such changes, reflecting a strong influence of drug load on polymer cracking. As can be seen in Fig. 7, the logarithmic plot of stationary release rate (Rs) versus drug load is significantly linear ($P < 0.001$) in the range explored with either elution medium, implying that a definite relationship of the type $Rs \propto (Load)^n$ should hold within this interval. The exponent, n, calculated as the slope of the log–log plot, is 2.95 for the buffered medium and 2.84 for the unbuffered one. Such a similarity of values indicates that the receptor medium effect is substantially unmodified by changes in drug load.

Effect of drug particle size

When drug powder in a finer size range than the commercial product (mean volume diameter 30 μm vs 90 μm) was used to load the matrices, not only was the release rate, but also the pattern was influenced by the load. This is clearly shown in Fig. 8 by data obtained with the re-crystallized product. A pseudo-zero-order release pattern is

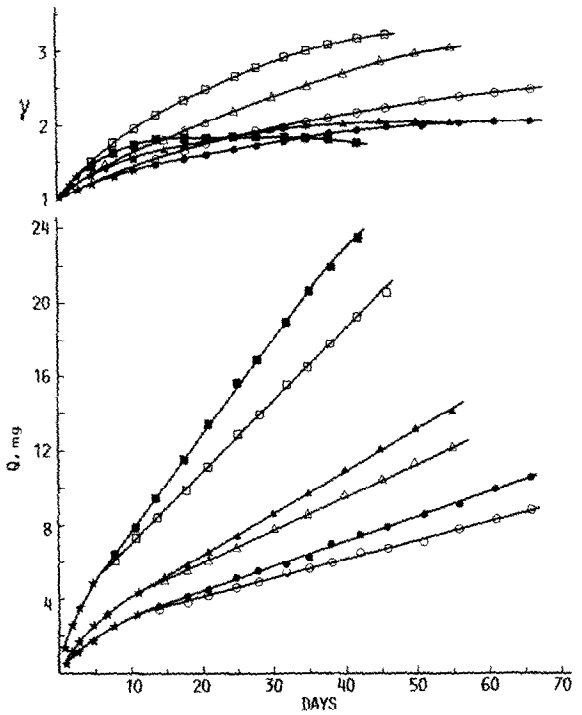

Fig. 6. Influence of drug load on clonidine hydrochloride release from cylindrical PDS pellets (Q, cumulative amount released), and corresponding matrix swelling kinetics (γ, ratio of swollen-to-dry matrix weights). With each load matrices from a single batch were eluted in phosphate buffer pH 7.4 (open symbols) or normal saline (full symbols). Key: ○ ●, 25%; △ ▲, 30%; □ ■, 40%; ★, superimposed points.

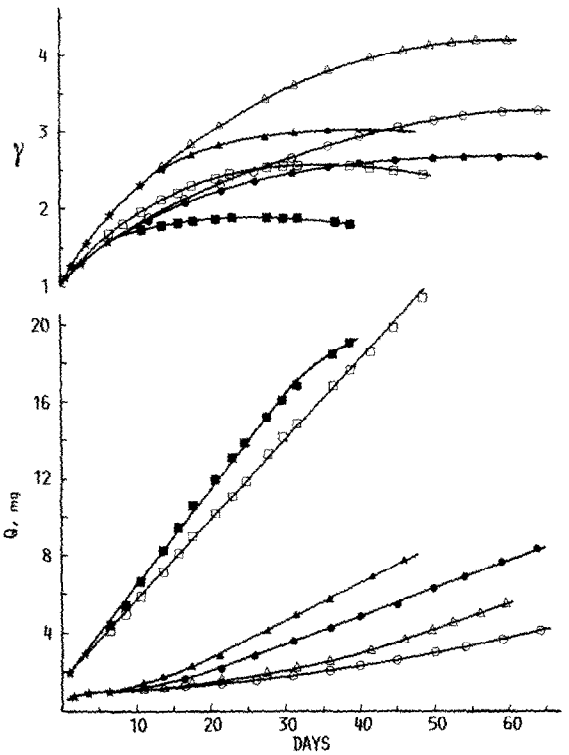

Fig. 8. Influence of drug load on release of re-crystallized clonidine hydrochloride from cylindrical PDS pellets (Q, cumulative amount released), and corresponding matrix swelling (γ, ratio of swollen-to-dry matrix weights). With each load matrices from a single batch were eluted in phosphate buffer pH 7.4 (open symbols) or normal saline (full symbols). Key: ○ ●, 20%; △ ▲, 25%; □ ■, 30%; ★, superimposed points.

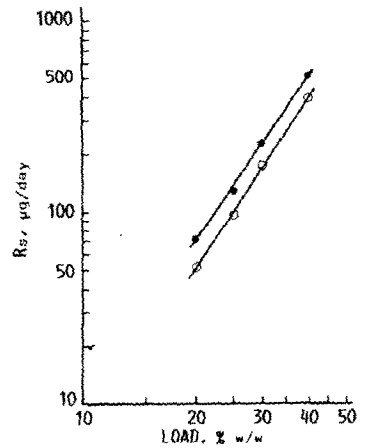

Fig. 7. Log–log plot of Rs values of Table 2 for the cylinders plotted against drug load. Key: ○, phosphate buffer pH 7.4 as receptor medium; ●, normal saline as receptor medium.

indeed observed only with 30% load, whereas with lower loads the release curves show an upward bending. In these cases lower release rates and higher matrix swelling degrees are observed at early times compared with the corresponding data with the coarser powder (compare relevant data in Figs. 8 and 6), which can be interpreted as if a time lag was needed for the more dispersed osmotic agent to start polymer cracking. As the osmotic particles were brought nearer by raising the load to 30% no such lag time was any more needed and a pseudo-zero-order release kinetics with about twice as high a rate as with the coarser product soon set in. Matrices with 40% load of re-crystallized product were also tested, but no reproducible release or swelling data could be obtained.

Conclusions

The present monolithic devices have shown unique performances which were concurrently elicited by the peculiar osmotic activity of clonidine hydrochloride and physico-mechanical properties of the PDS polymer. The physical model underlying the pseudo-zero-order release kinetics observed with the devices is rather complex and has not been fully clarified, although some insight into the events that control release was obtained. Experimental study of such relevant factors as drug particle size and load and matrix shape has allowed the following information to be concluded about the conditions for achieving apparent zero-order release kinetics and the variables for modulating release rate and time scale.

(a) Constant-rate delivery only requires control of drug particle size (the commercial product has turned out to be in a most appropriate range) and mechanical properties of polymer. We have shown that the filler usually used to reinforce the PDS elastomer plays a relevant role in controlling release in that it limits crack propagation in the solvent-stressed polymer.

(b) Changes in matrix shape (disk vs cylinder) or drug loading dose are inconsequential to the release pattern if drug powder in the commercial size range is employed.

(c) A strong influence of drug load on release rate, as quantified by a highly significant log–log correlation, allows rate to be modulated over a wide range of pharmacologically interesting values.

The apparent zero-order regimen, which can be made to last several months, is generally preceded by a burst effect and followed by a decline of rate when osmotic pumping ends up and the matrix starts shrinking. By this time around 50% of initial drug load has been released. The receptor medium effects observed in the present study anticipate some influence of the pH and buffering competence of physiological fluids on release rate.

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