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FORMULATION OF SILICONE MATRIX SYSTEMS FOR LONG TERM CONSTANT RELEASE OF PEPTIDES

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ABSTRACT

Theoretically, release of drug through the water-filled pores of matrix systems is expected to show a square-root-of-time dependence, with time exponents of 0.5 and hence continuosly declining release rates. Yet there have been many research groups finding remarkable deviations.
The aim of this work was to investigate on factors which lead to deviations from the square-root-of-time law and may be helpful for the development of matrix systems with constant drug release for long time.
Matrices of polydimethylsiloxane (PDMS) were prepared incorporating varying amounts of different pore-building, water soluble hydrogels. The hydrophilic model drug was Gly-Tyr.
The following essential factors influencing the long-term release profiles were found: (i) total matrix loading, (ii) its dissolution rate and (iii) the viscosity of the pore-building hydrogel. A proper choice of conditions lead to release profiles with time-exponents up to 0.8 for a time period of several weeks.

INTRODUCTION

Long-term controlled release of drugs from inert matrices has been subject of numerous scientific investigations (1-7). The easily manufactured release systems may be applied as subcutaneous implants in humans and for veterinary use. They are helpful in many other areas too, as for instance in agriculture (8).

THEORY

As for long-term release a comparatively high drug dose is required, drug concentration in the device will in most cases exeed matrix solubility by far. Theoretical considerations may therefore be reduced to suspension-type matrix systems (9, 10).

Dealing with the release of a peptide, or generally spoken of hydrophilic, water soluble drugs, drug release will occur by pore-diffusion. The pores may be part of the matrix itself or they may be formed in situ, as drug particles are leached out by the penetrating aqueous medium (11). Provided that (i) water penetration and drug dissolution are much faster than pore diffusion, (ii) matrix pores are only built in situ, while (iii) matrix diffusion be negligible, time dependent release is described by eq. (1).

$$M(t) = F \sqrt{(2A - \epsilon C_S) \frac{D}{\tau} C_S \, t} \qquad (1)$$

M: Amount of drug released
F: Surface in contact with release medium
A: Drug concentration in matrix (Matrix loading)
ϵ: Porosity of matrix
C_S: Drug solubility in matrix pores
τ: Tortuosity factor of matrix pores
D: Diffusion coefficient of drug in matrix pores

TABLE 1

Review of Publications on Release of Hydrophilic Drugs from Matrix Systems, mostly showing Deviations from the Square-root-of-time Law

Drug/ Excipient in Matrix	Matrix-Polymer	Release-Profiles Observed/ Interpretation	Reference
Chloroquine-Diphosphate/ None	PDMS[1]	Burst, than fairly constant rates (4 months)	Fu et al. 1973 (1)
Morphine-Sulfate/ Sodium-Alginate	PDMS	Second Order/ Matrix-swelling may be the reason	Mc Ginity et al., 1979 (12)
Different Proteins	EVA[2]	Sigmoidal, biphasic or $\sqrt{t}$/ Matrix-swelling may be the reason for deviations	Langer et al., 1978 (13) Langer, 1982 (14)
Sodium-Salicylate/ PEG	PDMS	Sigmoidal, eventually zero-order/ Matrix-swelling is responsible	Di Colo et al., 1983 (15)
Bovine-Serum-Albumin	PDMS	Burst, than fairly constant rates (3 months)	Hsieh et al. 1985 (16)

[1] Polydimethylsiloxane, [2] Ethylene vinyl acetate

Unfortunately, the square-root-of-time dependence described by eq. (1) is inconvenient especially for long-term drug delivery as release rates strongly decline with time. On the other hand, there are numerous publications on matrix type release systems showing remarkable deviations from the expected square-root-of-time

law (Table 1). Deviations are mainly observed when water soluble drugs are delivered. It may further be noticed, that presumably most of the corresponding experiments are based on the use of PDMS as matrix polymer. As indicated by Table 1, in many cases matrix swelling is suggested to be the reason for the unexpected release profiles. Di Colo et al. (15) succeeded to show that water uptake into the matrix may indeed have strong influence on release kinetics.

MATERIALS, METHODS

The following items were used:
- Matrix polymer: PDMS (Silastic^{R} 382 Medical Grade Elastomer, Dow Corning Corp., USA-Midland, MI).
- Matrix embedding: PDMS (Silastic^{R} MDX-4-4210 Medical Grade Elastomer, Dow Corning Corp., USA-Midland, MI).
- Pore-building, hydrophilic excipient: Hydroxyethylcellulose (HEC), viscosity grades of 2% aqueous solution 300, 6000, 30000 mPas, (Natrosol^{R} 250 G, H, M, Hercules BV, NL-Den Haag).
- Pore-building, hydrophilic excipient: Bovin serum albumin (Sigma Chemical Company, USA-St. Louis, MO) of high and low dissolution rate. Dissolution rate of the product obtained could be extremely reduced by a special treatment.
- Gly-Tyr (Fluka AG, CH-Buchs), as model drug.

Drug and excipients were sieved to abtain a particle size between 45 and 90 μm. Than model drug Gly-Tyr and excipient were thoroughly dispersed in Silastic^{R} 382 plus curing agent. Dispersions were quickly transferred to a mold. After curing (24 h, 40 ^{o}C) a sheet of 1.5 mm thickness was obtained; discs of about 6 mm in diameter were cut out. Matrices were embedded in Silastic^{R} MDX leaving one planar surface uncovered to meet the conditions of eq. (1). The concentration of Gly-Tyr was

kept at 5% (w/w), whereas the concentration of excipient varied between 25 and 45% (w/w); thus, matrix-loading was between 30 and 50% (w/w). Release experiments were performed under sink conditions in vials containing 10 ml of isotonic phosphate buffer pH 7.4, at 37°C. The experiments lasted 3 to 4 weeks with the media completely exchanged every two to three days. Upon exchange of release media, matrix-swelling was observed by thoroughly weighing the embedded matrices.

Release profiles were characterized by fitting the time-exponent equation (eq. (2)) to the data. Eq. (2), which also includes eq. (1) empirically describes release profiles of matrices deviating from eq. (1). Release exponents n greater than 0.5 indicate time-dependent variation of parameters in eq. (1) which lead to a more constant drug delivery (17).

$$M(t) = a\ t^{n} \qquad (2)$$

M: Amount of drug released
a: Kinetic constant
n: Release exponent

In several cases, a fit of eq. (2) to the data was not statistically significant, or the residuals indicated systematic deviations due to strongly bended release profiles. Then, alternatively a fit of eq. (3) was tried in order to be able to describe tendencies which occur upon variation of matrix composition. In all cases the first time interval was not considered, as burst-effects are to be expected which are not representative for long-term drug release.

$$M(t) = m\ (1 - \exp(-k\ t)) \qquad (3)$$

M: Amount of drug released
m: Kinetic constant
k: Release constant

RESULTS

Matrices containing HEC

The results for matrices containing HEC as excipient are shown in Table 2 and Figs. 1 and 3. Table 2 shows, that only at the lowest matrix loading (30% (w/w)) eq. (2) could be fitted to release data. It may further be seen, that at this loading level release exponents n always yield values which exceed the value of 0.5. In one case a release exponent of 0.79 is obtained. For higher matrix loading eq. (3) obviously fits better to release data. It is expected, that the curvature of release profiles and hence the tendency to release rate decline are too strong as to be fitted to eq. (2). At a matrix loading of 50% (w/w) (in one case even at 40% loading) any fit was impossible due to quick matrix depletion. Finally, as expected, the average release rate strongly increases at higher matrix loading. Table 2 and Fig. 3 further show the influence of excipient viscosity grade on matrix release: it may be seen, that increased excipient vicosity always leads to stronger declining release rates. At 30% (w/w) loading level increased excipient viscosity leads to a marked reduction of the release exponent n. At the 40% loading level the same tendency is observed, as expressed by the release constant k which increases upon excipient viscosity. In all cases, also the average release rate is affected. It is strongly reduced when excipient viscosity increases. Due to quick matrix depletion, effects could not be evaluated for 50 % (w/w) matrix loading.

Matrices containing BSA

The results for matrices containing BSA are shown in Table 2 and Fig. 5. A strong influence of the excipients dissolution rate on release kinetics may be seen. Release exponents n are obtained which are markedly higher than 0.5. Yet, at 50% (w/w) loading the residuals suggest small but systematic deviations from

TABLE 2

Results of fitting Parameters a, n of Eq. (2) or Parameters l, m of Eq. (3) to Release Data of Matrices containing HEC or BSA. Results are not mentioned, if Fits were impossible. Inferior Results in Parenthesis.

Matrices containing HEC:

Viscosity Grade (mPas)	Matrix Loading (% (w/w))	Parameter Values Eq. (2) a	n	Eq. (3) l	m
300	30	50.1	0.792		
6000	30	25.9	0.606		
30000	30	13.2	0.556		
300	35	(147.5	0.652)	1417	0.067
300	40	Fast depletion of matrix			
6000	40	(122.6	0.647)	1206	0.063
30000	40			870	0.115
	50	At all Viscosity Grades Fast depletion of matrix			

Matrices containing BSA:

Dis-solution Rate	Matrix Loading (% (w/w))	Parameter Values Eq. (2) a	n	Eq. (3) l	m
High	40			1099	0.181
High	50	Fast depletion of matrix.			
Low	30	Amounts released within tolerance of HPLC-assay.			
Low	40	36.0	0.750		
Low	50	(82.3	0.800)	1607	0.040

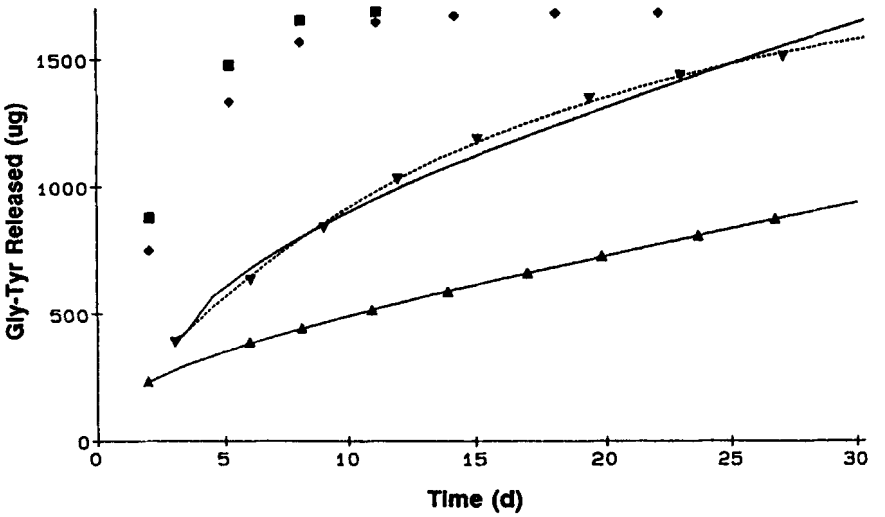

FIGURE 1

Gly-Tyr release from PDMS-matrices containing HEC, viscosity grade 300 mPas. Matrix-loading ▲ 30%, ▼ 35%, ◆ 40%, ■ 50% (w/w). ——Fit of eq. (2), - - - eq. (3). Mean values, n=3.

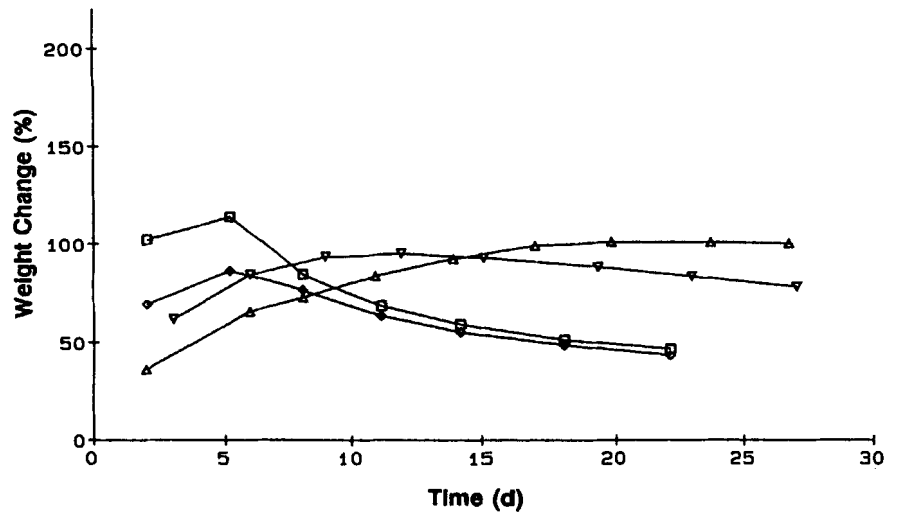

FIGURE 2

Weight change (% (w/w)) during Gly-Tyr release from PDMS-matrices. Matrix excipient HEC, viscosity grade 300 mPas. Matrix-loading △ 30%, ▽ 35%, ◇ 40%, □ 50% (w/w). Mean values, n=3.

eq. (2) and eq. (3) is fitted better after about 2 weeks. Average release rates are strongly reduced when slowly dissolving excipient is used.
In contrast to matrices containing (quickly dissolving) HEC, average release rates for slowly dissolving BSA are very slow even at 50% (w/w) loading; release rates for 30% matrix loading were so small, that amounts released were almost within the tolerance of the HPLC-assay. With quickly dissolved BSA, matrices behaved similar to devices containing HEC.

RELEASE MECHANISM

The results show, that in no case release profiles followed the square-root-of-time equation (eq. (1)). A marked influence of the excipients viscosity grade or dissolution rate on drug release is further observed. The swelling profiles for matrices containing low-viscosity HEC or BSA are shown in Figs. 2, 4 and 6. The profiles show, that a maximum of swelling profiles is always observed in cases of quick drug depletion and strongly bent release curves. Only in cases, where maxima of swelling profiles are not or hardly not observed the corresponding release profiles show reduced decline of release rates. The results further show, that for quickly dissolving excipient (HEC) low matrix loading is a prerequisite for fitting eq. (1) and getting release exponents greater 0.5. For slowly dissolving BSA however, reduced decline of release rates may also be obtained at high loading levels up to 50% (w/w). Finally, a gravimetric assay of matrices shows, that the residence time of excipient is markedly prolonged if matrix loading is low or if dissolution rate of excipient is reduced (Table 3).
These observations suggest, that a prerequisite for

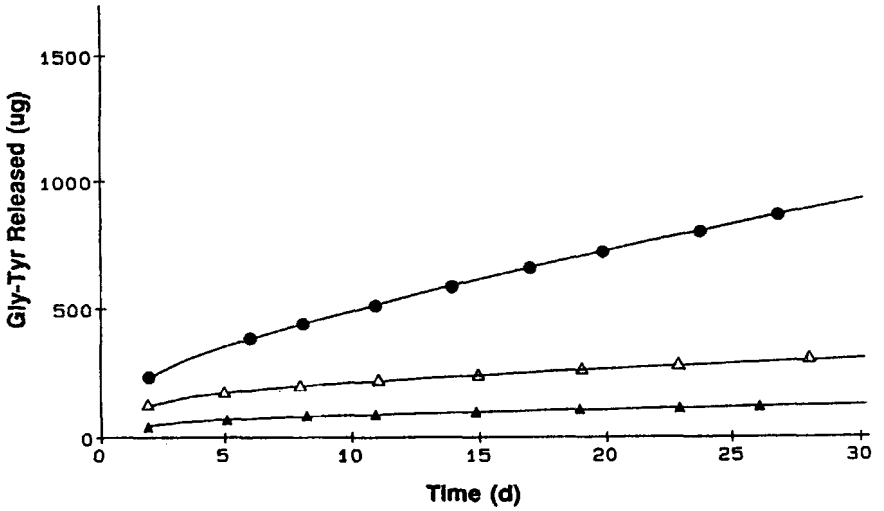

FIGURE 3

Gly-Tyr release from PDMS-matrices containing HEC, matrix loading 30% (w/w). Viscosity grade of excipient ● 300, △ 6000, ▲ 30000 mPas. —— Fit of eq. (2). Mean values, n=3.

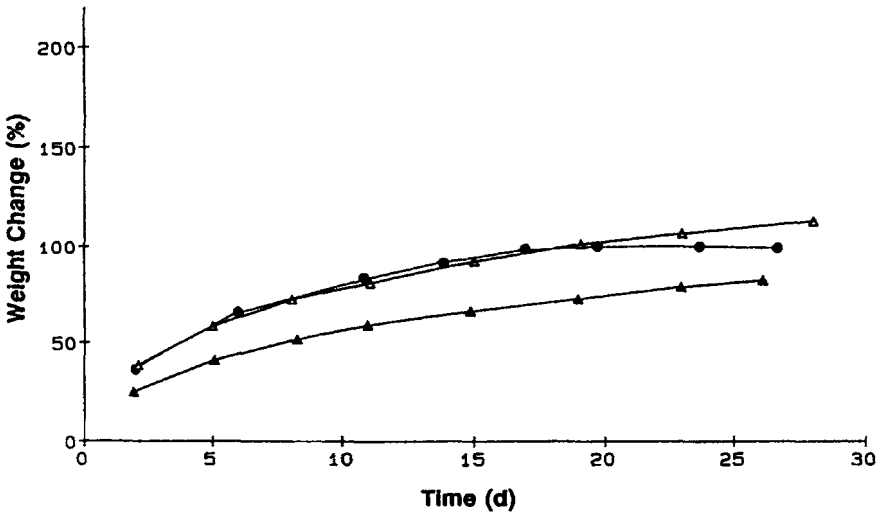

FIGURE 4

Weight change (% (w/w)) during Gly-Tyr release from PDMS-matrices containing HEC. Matrix loading 30% (w/w). Viscosity grade of HEC ● 300, △ 6000, ▲ 30000 mPas. Mean values, n=3.

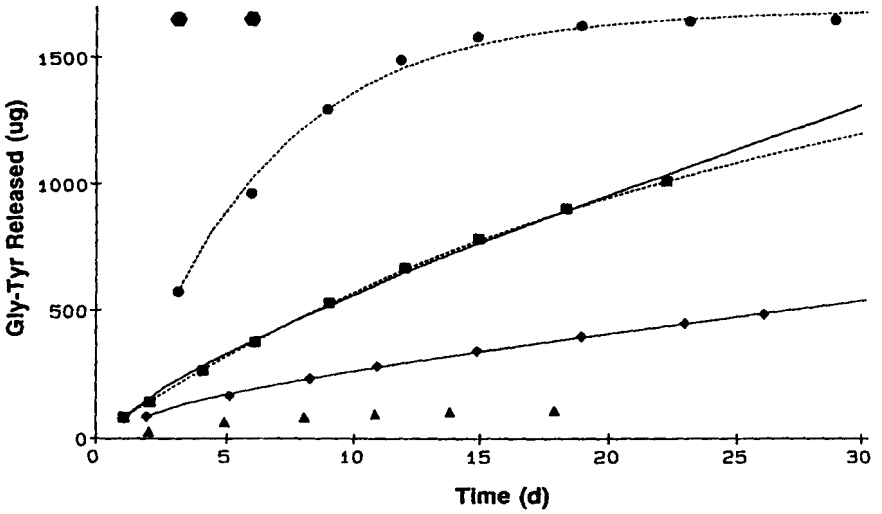

FIGURE 5

Gly-Tyr release from PDMS-matrices containing BSA. Quickly dissolving BSA, matrix loading ● 40%, ● 50%. Slowly dissolving BSA, loading ▲30%, ◆ 40%, ■ 50% (w/w). Fit of—— eq. (2),- - - eq. (3). Mean values, n=3.

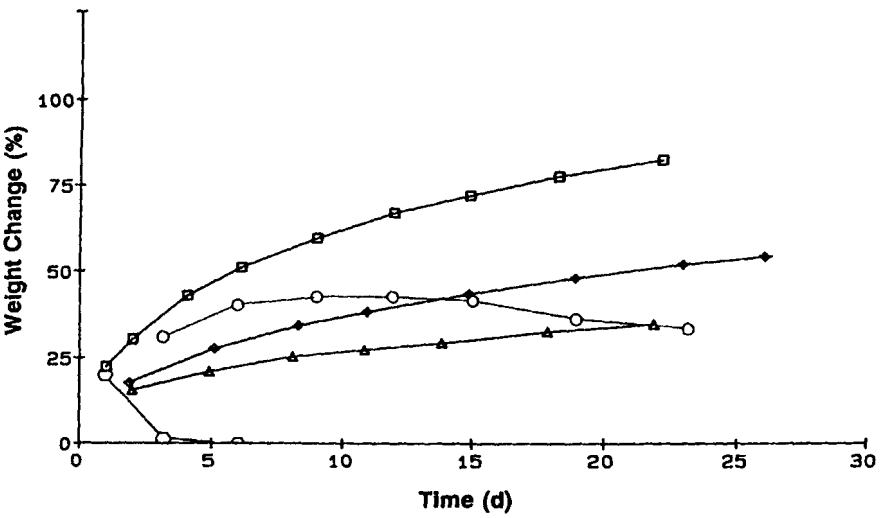

FIGURE 6

Weight change (% (w/w)) during Gly-Tyr release from PDMS-matrices containing BSA. Quickly dissolving BSA, matrix loading ○ 40%, ⬡ 50%. Slowly dissolving BSA, loading △ 30%, ◇ 40%, □ 50% (w/w). Mean values, n=3.

TABLE 3

Residual Amount of Excipient and Water Content of remaining Excipient in Matrix after 16 Days of Release. Gravimetric assay, n=2.

Excipient HEC: Viscosity Grade (mPas)	Matrix Loading (% (w/w))	Excipient after 16 Days: Residual Amount (% (w/w))	Water Content (% (w/w))
300	30	92.0	82.4
6000	30	92.6	82.4
30000	30	92.3	74.4
300	40	73.9	83.4
6000	40	72.9	81.6
30000	40	73.5	85.2
Excipient BSA: Dis-solution Rate	**Matrix Loading (% (w/w))**		
High	50	56.1	64.8
Low	50	92.3	64.3

getting long-term drug release and release exponents above 0.5 is long-term remainder of the excipient within the pores. Obviously, the hydrated, hydrocolloid type excipients in the matrix pores act as diffusion medium for the drug.

In the case of high dissolution rate of excipient and/or high matrix loading, strong initial swelling, quick depletion of matrix excipient and consequently depletion of the elastic matrix pores occur. This should lead to strongly bent release curves. It is noteworthy, that swelling maxima have no influence on release profiles; so obviously, excipient is released from zones of the matrix already drug-depleted.

On the other hand, when the excipient is leached out slowly, long-term swelling within the pores obviously contributes to time dependent changes of parameters from eq. (1). This may lead to release exponents exceeding the value of 0.5. Especially, the diffusion coefficient D may increase upon swelling (18); as shown in Table 2 and Fig. 3, a suitable vicosity grade is essential for convenient release profiles. Also increasing drug solubility C_S within the pores, increasing porosity ϵ or decreasing tortuosity τ may counteract the tendency to release rate decline.
So, constant long-term release from matrix systems may preferably be realized under the following conditions: (i) hydrocolloids should be used as pore-forming excipients, (ii) excipients should be leached out very slowly, (iii) the matrix polymer should be elastic and permeable to water vapour in order to permit swelling and yield homogeneous water uptake. Finally (iv) the swelling, drug saturated excipient should be of higher osmotic activity than the surrounding medium in order to permit water uptake.
The results show, that this concept is capable of long-term "anomalous diffusion" (17). Further optimization may lead to matrix-type release systems capable of even longer and more constant drug release.

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