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The megaloporous system: a novel principle for zero-order drug delivery. II. A model for the mechanism of drug delivery

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Summary

The megaloporous system is composed of two phases with different liquid-penetration properties (the housing matrix phase and the restraining matrix phase) and delivers most of its drug content at a zero-order rate. The mechanism of drug release from the system is based on the concept of a *decrease* in the *rate* of surface area exposure in time of the restraining matrix phase (containing the drug) to the penetration liquid with simultaneously an *increase* in time of the *total* restraining matrix phase *surface area*, contributing to the delivery process. This model is mathematically represented by a convolution integral. It provides an explanation for the substantially constant release characteristics of drug from the megaloporous system. By using empirical equations in the convolution integral for the rate of restraining phase unit supply to the extraction liquids and for the drug release function of one restraining phase unit, it can be concluded that the model adequately describes the release principle of the megaloporous system.

Introduction

Preparations composed of granules with different drug release rates have been described in patent literature (Leslie, 1976; Hamada, 1959; Kornblum and Stoopak, 1977). Drug delivery from the slow release dosage forms is described as the result of controlled disintegration of the tablets. By the slow disintegration process, particles containing drug are released to the entire digestive tract.

In this study a new drug-delivery system, referred to as the megaloporous system, is introduced. The device yields substantially zero-order release characteristics and is easily constructed. In a previous paper (De Haan and Lerk, 1986) the in vitro and in vivo performance of two compositions of the megaloporous system have been evaluated.

The megaloporous system can be viewed principally as a single unit device comprising two structures with essentially different penetration characteristics for the extraction liquids. The structures operate together to transfer drug from the dosage form with a constant rate to the dissolution liquids over an extended period of time. The one structure is called the *restraining matrix phase* and comprises the drug and a release rate controlling material. The other structure is the *housing matrix phase* and contains a penetration rate controlling material. Furthermore, this phase

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develops a system of interconnected *large pores*. The object of the present study was to develop a model for the mechanism of drug release from the megaloporous system in order to find an explanation for the constant release characteristics.

Materials and Methods

The two types of granules used in this study: the housing matrix granules (HMG) (formulations in Table 1); and the restraining matrix granules (RMG) (formulations in Table 2) were prepared as described in a previous paper (De Haan and Lerk, 1986).

Preparation of tablets

A mixture of both types of granules was prepared by intimately mixing 0.460 g of the restraining matrix granulation with 0.530 g of the housing matrix granulation, corresponding to 195 and 105 mg (or 0 mg) of theophylline, respectively.

Tablets, weighing 990 mg each, were compressed on an instrumented hydraulic press (Hydro Mooi, Appingedam, The Netherlands), using 13 mm diameter flat-faced punches at an upper punch compaction pressure of 73.9×10^3 kN · m^{-2}.

Compacts, to be inserted in the perspex tube (Fig. 1), were prepared by compressing an appropriate amount of granulation mixture at an upper punch compaction pressure of about 18.5×10^3 kN · m^{-2}. The compact formed was placed in a tube (internal diameter 13.0 mm) with the surface, to be exposed to the dissolution medium, 2 mm from the lower tube surface and then compressed at a pressure of 73.9×10^3 kN · m^{-2}. Disks, containing restraining matrix units, embedded about 1 mm from the flat outer surface, were prepared by carefully positioning four restraining particles (approximately equal in weight and form) on housing granulate and then by covering the units with a determined weight of housing phase material. Compression and insertion in the perspex tube was performed as described for the compacts.

For both the compacts and the disks, visual examination indicated that practically no air was enclosed between the lateral tablet surface and the tube wall. The upper tablet surface was completely covered with molten hard paraffin to simulate penetration conditions of a tablet completely immersed in the extraction liquids (Fig. 1).

TABLE 1

FORMULATIONS OF THE HOUSING MATRIX GRANULATION (HMG)

	HMG				
	I	II	III	IV	V
Theophylline monohydr. (Ph.Eur)	21.7 [1]	–	–	–	–
Carboxyvinyl polymer [2]	7.5	7.5	5.0	2.0	–
Polyethylene glycol 6000	35.2	35.2	35.2	35.2	35.2
Lactose EFK [3]	36.6	58.4	58.4	58.4	58.4
Magnesium stearate	1.8	1.8	1.8	–	–

[1] In grams.
[2] Carbopol 934, B.F. Goodrich Chemical Co.
[3] H.M.S. Bolsward, The Netherlands.

TABLE 2

FORMULATIONS OF THE RESTRAINING MATRIX GRANULATION (RMG)

	RMG		
	I	II	III
Eudragit L [2]	–	15.0	–
Eudragit RSPM [2]	25.0 [1]	–	25.0
Theophylline monohydr. (Ph.Eur)	44.0	44.0	–
Cetyl alcohol	5.0	–	5.0
Talc	25.0	–	25.0
Emcompress [3]	–	40.0	–
Acetone	–	100	–
Chloroform	100	–	50

[1] In grams.
[2] Röhm Pharma, Darmstadt, F.R.G.
[3] Mendell Co., New York, U.S.A.

In vitro dissolution testing

The in vitro release of theophylline was measured using the USP XX paddle apparatus at 100 rpm. The tablets and the restraining granules (460 mg; about 220 particles) under investigation were placed in 0.1 N hydrochloric acid (900 ml), maintained at 37 ± 0.5°C. Samples of the dissolution medium were removed periodically from the

beaker and replaced with dissolution medium. The samples were filtered and after dilution assayed with a Beckman Spectrophotometer for their theophylline content.

In the release profiles given, the highest and the lowest values and the mean are presented at each dissolution time. To determine the rate of drug release from one flat surface of the compact or disk, the cylindrical preparation was inserted in a perspex tube, as mentioned previously. The tube was introduced into the solvent through a hole at 2.5 cm from the centre of the paddle shaft and clamped so that the tablet surface exposed to the dissolution medium was 1.0 cm below the level of the solvent to ensure water penetration (Fig. 1).

Prior to the start of a determination, the air-bubble entrapped by the part of the perspex cylinder beneath the cylindrical preparation was removed completely by tapping carefully.

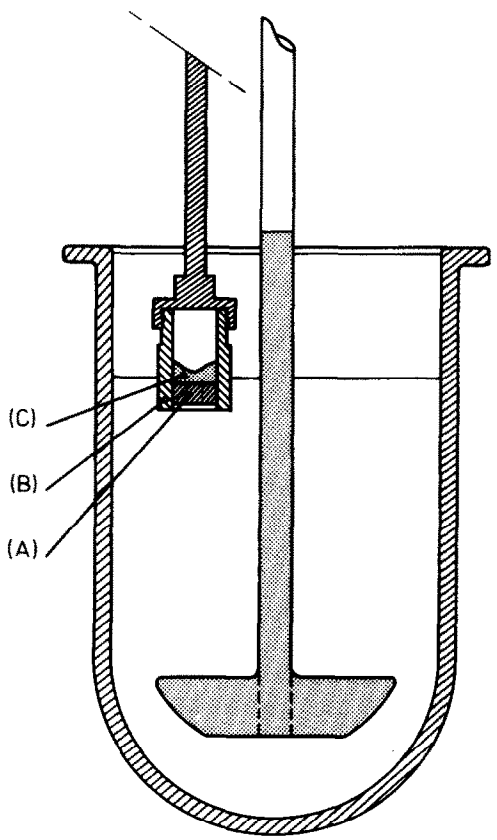

Fig. 1. Paddle apparatus with a megaloporous device (A), mounted in a perspex tube (B). Hard paraffin (C).

Drug extraction from four restraining particles, embedded at a distance of about 1 mm from the disk outer surface contacting the extraction liquids, was performed as described earlier, with the exception that only 400 ml of 0.1 N hydrochloric acid was used.

Modelistic approach of the drug delivery mechanism

Devices, prepared from a mixture of large granules (about 0.5–2 mm), may be considered as megaloporous systems, when extraction of the high content of soluble excipients from the housing phase provides *very large pores* (about 1 mm) in the skeleton, which is formed by the insoluble ingredients of the restraining phase.

The *housing phase* should always be continuous and should principally control the rate of liquid penetration into the system. The *restraining matrix phase* comprises the drug and may be continuous to constitute a skeleton of insoluble materials in order to resist mechanical stress applied to the device during drug delivery.

The megaloporous system, after a lapse of finite time of immersion in the dissolution medium is depicted schematically in Fig. 2.

Drug release from such a system is a function of: (1) the extraction of drug from a restraining phase unit (p(t)); and (2) the rate at which the restraining phase units are supplied to the liquid (dn(t)/dt). If it is assumed that the extraction

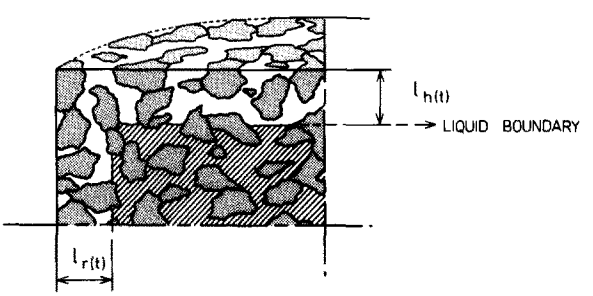

Fig. 2. Schematic diagram of a partly extracted megaloporous system. Restraining matrix phase, ▩; housing phase, ▨; depleted part of the housing phase □.

function from each restraining phase unit of the megaloporous skeleton is equal, then drug release from the megaloporous system may be described by the convolution integral:

$$y(t) = \int_0^t p(t-\tau) \cdot \frac{dn(\tau)}{d\tau} \cdot d\tau \qquad (1)$$

The functions p(t) and dn(t)/dt can be measured independently for a certain system.

(a) The function p(t)

An equation describing the drug remaining in a spherical matrix particle as a function of immersion time, and based on diffusion, has been developed by Higuchi (1963). One of the reasons for not applying the expression in this study is the irregular shape of the restraining phase units. We preferred to use an experimental equation of the form:

$$p(t) = C \cdot t^n \qquad (2)$$

This equation is found to afford a feasible relationship up to about 90% of the drug released.

(b) The function dn(t) / dt

The generation of restraining phase units is governed by the housing phase. Its soluble components allow the liquid to penetrate the megaloporous system. The extraction process of the soluble excipients provides very large pores in the system.

As the extraction rate dW(t)/dt of the soluble excipients determines the rate at which the restraining phase units are exposed to the liquids,

$$\frac{dn(t)}{dt} = K \cdot \frac{dW(t)}{dt} \qquad (3)$$

and

$$N(t) = K \cdot W(t) \qquad (4)$$

in which K is the number of restraining matrix particles per unit weight of soluble housing phase material, N(t) is the number of restraining matrix particles exposed to the liquid at time t and W(t) is the weight of soluble material of the housing phase dissolved at time t.

The parameter dn(t)/dt is evaluated in terms of overall retreat rate of the liquid boundary in the housing phase and the dimensions of the system. When the overall retreat rate of the liquid boundary perpendicular to the radius ($1_{h(t)}/t$) and the overall retreat rate perpendicular to the planar surface of the cylindrical system ($1_{r(t)}/t$) are assumed to be equal, then the height (h(t)) and the radius (r(t)) of the cylindrical-shaped residue of the undissolved housing phase at t (min) is given by the Eqns. 6a and 6b:

$$\bar{v}(t) = 1(t)/t \qquad (5)$$

$$h(t) = h_0 - 2\,\bar{v}(t) \cdot t \qquad (6a)$$

$$r(t) = r_0 - \bar{v}(t) \cdot t \qquad (6b)$$

where $\bar{v}(t)$ is the overall retreat rate of the liquid boundary at t, 1(t) is the penetration depth of the liquid boundary at t, h_0 is the height of the cylindrical system at $t = 0$ and r_0 is the radius of the cylindrical system at $t = 0$. The weight of dissolved housing phase (W(t)) is given by:

$$\begin{aligned} W(t) &= f_{Vh} \cdot \rho_m \cdot \left(\pi r_0^2 h_0 - \pi r(t)^2 h(t)\right) \\ &= f_{Vh} \cdot \rho_m \cdot \pi \left((h_0 + r_0) \cdot 2 r_0 \bar{v}(t) t \right. \\ &\quad \left. - (h_0 + 4r_0)\bar{v}(t)^2 t^2 + 2\bar{v}(t)^3 t^3\right) \end{aligned} \qquad (7)$$

where f_{Vh} = the volume ratio of the soluble material in the housing phase of the system and the total volume of the system and ρ_m = the mean specific mass of the soluble material in the housing phase. If it is assumed that the rate of dissolution of the soluble excipients of the housing phase is proportionally related to the release rate of a suitable marker substance in the housing phase, then W(t) can be measured.

When Eqn. 7 is used to fit the experimental data points of the release of the marker substance, theophylline, from the housing phase, the overall retreat rate can be found as a function of time. The equation is also used to obtain the differentiated form dW(t)/dt from the experimental values found for W(t).

Results and Discussion

As pointed out in the introduction, the drug delivery system introduced consists of a penetration rate controlling housing phase, operating together with a drug restraining phase (Fig. 2), to result in a constant drug release from the total system. The housing phase granulate should constitute a continuous phase within the device. The resistance to the penetrating liquid, exhibited by the housing phase has to be substantially lower than the resistance, presented by the restraining phase.

Drug extraction from restraining matrix particles

The release profiles from the irregularly shaped restraining matrix units in the paddle model are shown in Fig. 3A. The figure also depicts the curve, found for a restraining matrix unit, embedded in a disk prepared from housing phase material, not containing theophylline. This procedure provides more realistic data for the estimation of the release function p(t) of a restraining matrix unit within the megaloporous system, as applied in Eqn. 1.

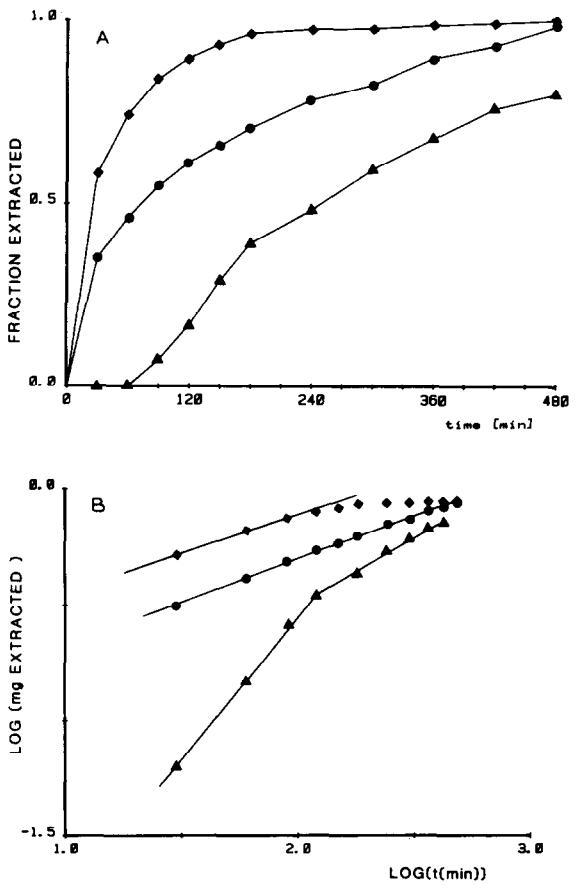

Fig. 3. A and B: Theophylline extraction from restraining matrix particles (paddle design). ◆——◆, RMG II; ●——●, RMG I; ▲——▲, RMG I particle embedded in HMG II.

TABLE 3

COEFFICIENTS AND EXPONENTS OF RESTRAINING MATRIX UNIT DRUG DELIVERY FUNCTIONS

	Coefficient	Exponent	Time period
RMG I	0.0904	0.37	0–480
RMG II	0.1459	0.37	0–130
	0.8864	0	130–480
RMG I embedded in HMG II	(lag-time)	–	60 min
	0.0009	1.26	0–120
	0.0232	0.57	120–420

Fig. 3B shows the release plots in a double logarithmic fashion. For the non-embedded particles linear relationships are obtained up to a drug delivery of about 90%. The extraction curve from this granulate is assumed to be representative for the "average" restraining particle. The coefficients and exponents, relating to Eqn. 2, are given in Table 3. One of the polymers applied in the restraining phase is Eudragit L, an anionic polyelectrolyte, which is insoluble in acidic aqueous solutions and soluble in neutral or weakly alkaline media by forming of salts. The other polymer, Eudragit RS, is insoluble in aqueous media, irrespective the pH.

For the embedded particle, an increase in drug release rate ($n = 1.26$) was found for a period of about 120 min after a lag-time of 60 min (Fig. 3A, Table 3). Finally, a decrease in release rate was found, resulting in biphasic release characteristics. The initial exponential increase in the rate of drug release found for the single embedded particle may be explained by the increase in time of the particle surface area exposed to the dissolution liquid. Also the formation of channels in the penetrated zone between the particle and the outer

surface of the disk may contribute to this phenomenon. In the time period necessary to complete dissolution, porosity in the area between the particle and the surface of the disk increases with time. The subsequent decrease in the release rate, resulting in biphasic extraction curves (Fig. 3A), probably refers to the period that the moving liquid boundary has passed the particle and major part of the soluble material between the restraining granule and the surface of the disk has been dissolved.

Unidimensional liquid penetration into the cylindrical system

For a better understanding of the mechanism of constant drug release from the complete system, containing both housing and restraining phase, the contribution of each of the phases within the device to the delivery process was studied separately.

First the situation of a constant rate of restraining matrix unit supply to the extraction liquids will be considered:

$$\frac{dn(t)}{dt} = R_i = \text{constant (units} \cdot \text{min}^{-1}) \qquad (8a)$$

The resulting drug release is mathematically expressed by the equation:

$$y(t) = R_i \int_0^t p(t-\tau) \cdot d\tau \qquad (8b)$$

When a drug extraction from individual matrices is taken into account (Table 3), this implies that the rate of drug release increases until the end of the leach of the first immersed restraining matrix unit. Calculated plots of the total release (y(t)) as a function of time as the result of application of the unit release functions of granulates RMG I, RMG II and embedded RMG I units (corrected for the lag-time) and a constant immersion rate ($R_i = 0.23$ unit $\cdot$ min^{-1}), are reflected in Fig. 4.

To simulate this procedure, a series of experiments was performed, reflecting the release of drug from one flat surface of the compact (Fig. 1). The release curves, obtained from combinations of one restraining phase formulation (RMG II) with different housing phase formulations, are reflected in Fig. 5. The plots demonstrate a more or less moderate increase in the rate of drug delivery, referring to an increase in surface area of the restraining phase, contributing to the release pro-

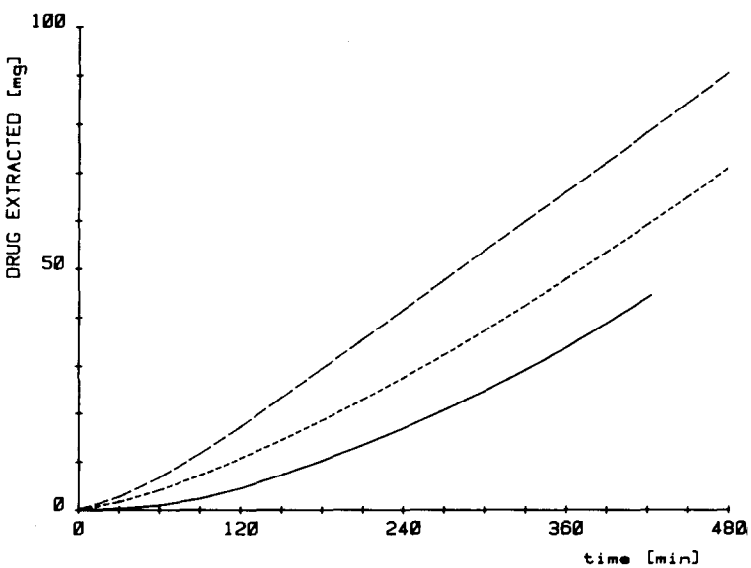

Fig. 4. Calculated release profiles, as a result of a constant rate of immersion (0.23 units $\cdot$ min^{-1}) of RMG II (— — — —), RMG I (– – – – –) and embedded RMG I units (———).

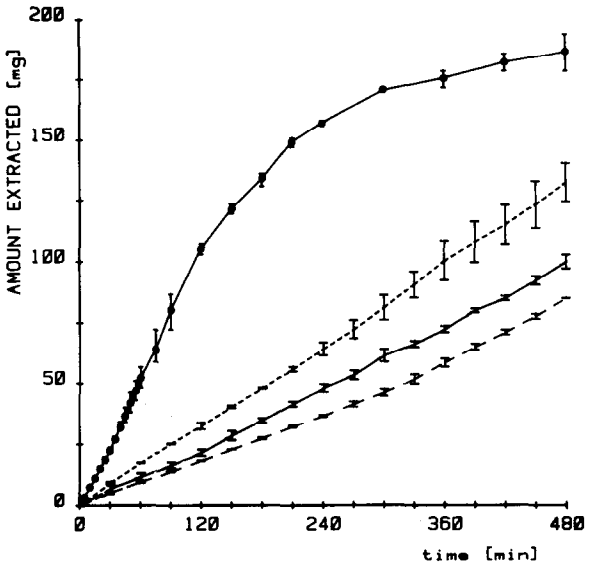

Fig. 5. Experimental drug release profiles from megaloporous systems with one flat surface exposed to the extraction liquids Combinations of RMG II with: HMG V ($n = 3$) ●———●; HMG IV ($n = 2$) - - - - - -; HMG III ($n = 2$) ———; HMG II ($n = 2$) — — —.

cess. For the combination with the fast dissolving housing phase formulation (HMG V), the rate of drug release finally declines, corresponding to the time period, that essentially all the restraining matrix-phase surface is participating in the drug delivery process. The results only permit a qualitative interpretation, as any swelling of the restraining matrix skeleton, due to the presence of water, would imply a decrease in the volume of the megalopores.

All-side liquid penetration into the cylindrical system

Drug release curves from completely immersed devices containing theophylline in only one of the composite phases are depicted in Fig. 6. The profile of drug extraction from the embedded restraining phase follows zero-order kinetics. The figure also shows the extraction profile from a system, with the drug only incorporated in the housing phase. The plot suggests a non-linear supply of restraining phase surface area to the extraction liquids. The decreasing rate of area supply is principally governed by the geometry of the system and by the penetration-controlling properties of the housing phase. The basic process of surface exposure of the restraining matrix skeleton is dissolution of the soluble ingredients from the housing phase by the surrounding fluid, which penetrates slowly into the system. Drug transport is assumed to occur principally through the liquid

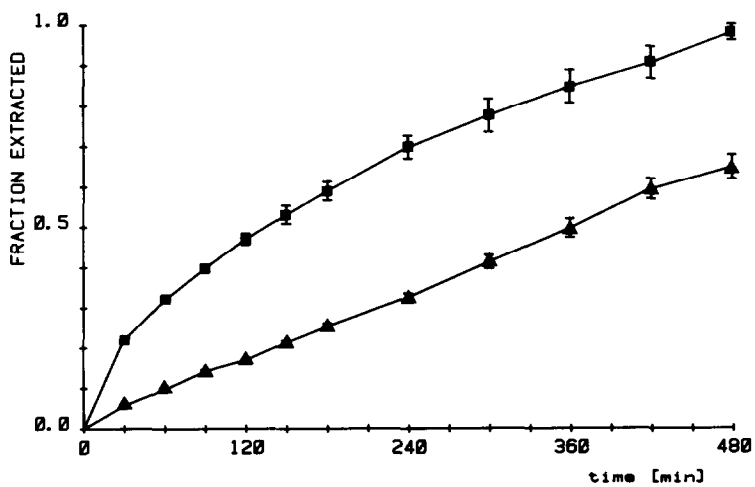

Fig. 6. Drug delivery profiles from each of the composite phases of the megaloporous system. ■———■, from housing phase HMG I in a system with no theophylline in the restraining phase (RMG III). ▲———▲, from restraining phase RMG I in a system with no theophylline in the housing phase (HMG II).

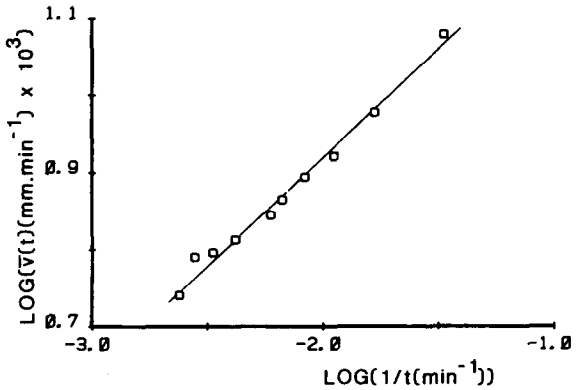

Fig. 7. A double logarithmic plot of the overall retreat rate of the liquid boundary ($\bar{v}(t)$) as a function of reciprocal time.

in the large pores, which are formed after depletion of the soluble material.

The theophylline release curve from the housing phase (HMG I) in the system (Fig. 6) is considered to describe the fraction of the surface area of the restraining matrix skeleton, exposed to the liquids in the megalopores with time. If Eqn. 7 is applied to fit the drug release curve from HMG I, there is found an overall retreat rate $\bar{v}(t)$, exhibiting an immersion time dependency (Fig. 7), which may be presented by:

$$\bar{v}(t) = 0.0303 \cdot t^{-0.2815} \quad (mm \cdot min^{-1}) \tag{9}$$

The number of restraining particles (N(t)) from the system comprising HMG I, exposed to the solvent as a function of time (Eqn. 4), becomes:

$$N(t) = 0.54 \times 10^{-4} \cdot t^{2.156} - 2.8 \times 10^{-2} \cdot t^{1.437} + 4.59 \cdot t^{0.719} \tag{10}$$

As reflected by Fig. 8, this equation fits the experimental data fairly well, when transformed into the fraction of drug extracted from the housing phase of the system. The figure also shows that a constant overall retreat rate of the liquid boundary in the housing phase of, as an example, 5.2×10^{-3} and 12.0×10^{-3} $mm \cdot min^{-1}$ did not provide suitable plots.

Based on the above results, the drug release from the megaloporous system (y(t)) can be calculated (Eqn. 1), with dn(t)/dt (obtained by differentiating Eqn. 10) as the restraining matrix unit generation rate and p(t) (Eqn. 2, Table 3) as the empirical drug release function from a unit of

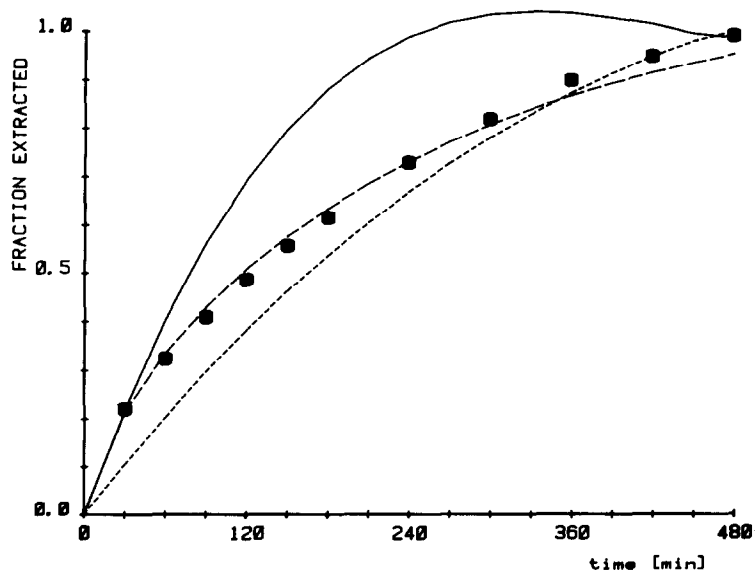

Fig. 8. Calculated drug release plots from the housing phase (HMG I) of a system. Applied overall retreat rate ($\bar{v}(t)$) of: – – – – –, 5.2×10^{-3} $mm \cdot min^{-1}$; — — —, $0.0303\ t^{-0.2815}$ $mm \cdot min^{-1}$; ———, 12.0×10^{-3} $mm \cdot min^{-1}$. The black spots are experimental data.

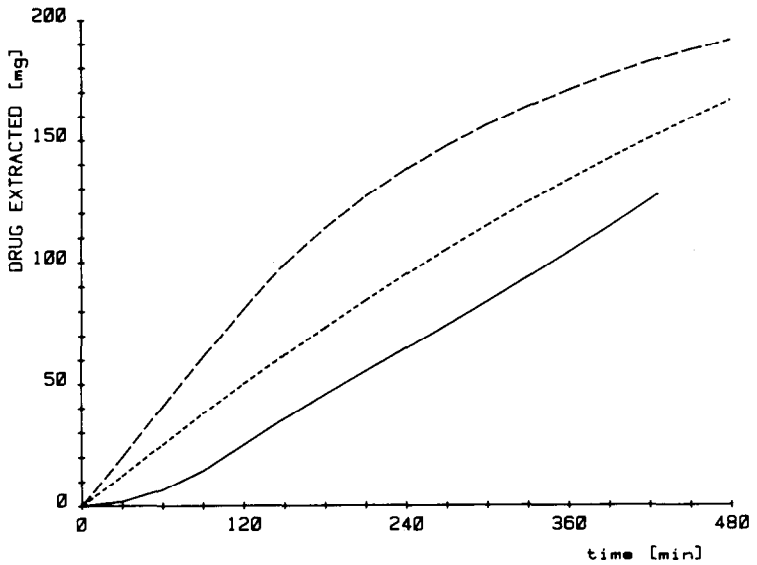

Fig. 9. Calculated drug release profiles, as a result of immersion of RMG II (— — — — —), RMG I (- - - - - -) and embedded RMG I particles (———), supplied to the penetrating liquids with the rate function from housing phase formulation HMG I, which is obtained by differentiating empirical Eqn. 10.

the restraining matrix phase. The results are plotted in Fig. 9. Over the range of 8 h, drug release deviates from linearity, particularly when the function of the fast release units (RMG II), which were not embedded, is applied. Aside from what appears to be an initial lag-time, however, for the embedded particles the plot yields a linear relationship up to at least 7 h. In this analysis, it is tacitly assumed, that all embedded restraining matrix units are located about 1 mm from the tablet

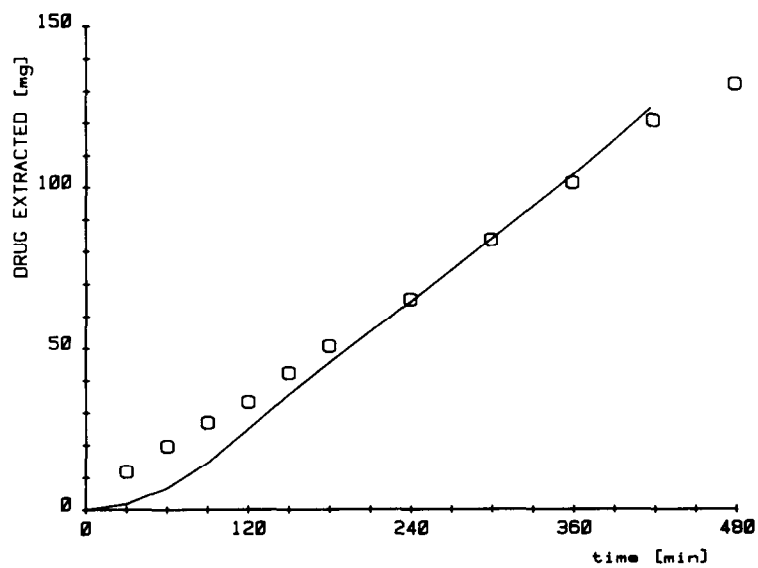

Fig. 10. Comparison of drug release data points from a megaloporous system containing restraining matrix phase RMG I and housing phase HMG II, with the calculated profile.

surface. This implies that no unit is present at the surface of the device to reduce the initial curvature. Though drug release from restraining matrix particles at different locations in the system will differ to some extent, the applied function p(t) for the embedded particle appears to be quite representative: the calculated and experimental results are in rather good agreement (Fig. 10). In the real system, however, a number of other factors may come into play, which may modify to some extent the total release behaviour.

Summarizing, the model for the release mechanism of drug from the megaloporous system is based on a gradually declining rate at which the restraining matrix particle surface is supplied to the extraction solvent with simultaneously, a cumulation of restraining matrix surface, contributing to the delivery process. For the studied megaloporous system, this results in a constant output of drug. The housing phase may be utilized to control the rate of liquid migration into the system and, by that means, to control the rate at which the restraining skeleton surface is exposed to the extraction liquids.

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