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CONTROLLED DRUG RELEASE FROM A COMPRESSED HETEROGENEOUS POLYMERIC MATRIX: KINETICS OF RELEASE

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ABSTRACT

A physical model of a new matrix-type system is presented where constant drug release can be maintained irrespective of the extent of the tortuosity and receding drug boundary. Theophylline base was dispersed as discrete crystals and fine particles in a matrix formed by the cross-linking of polymeric mixtures consisting of PEG, acrylic resins and ethyl cellulose. DSC analysis was performed to identify any solid state inactivation of the drug. Concave tablets at specified pressures were prepared in order to achieve a wide range of release rates and patterns of release. It was found that the patterns of release could be controlled by the formulation components and the manufacturing procedures. Drug release rates were determined spectrophotometrically under sink conditions and the flux of drug release,

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dQ/dt, from these matrix-type delivery systems was almost constant over 15 hours, during which time about 85% of the active drug was released. The release rate was devoid of any hydrodynamic boundary effect and environmental pH. The cumulative amount of drug released was found to be in accordance with zero-order kinetics. The system can be modified within broad limits and have flexibility as well as a wide spectrum of applicability with respect to different types of drugs.

INTRODUCTION

Drug action is related to its concentration at the receptor site and its pharmacokinetic fate. For drugs whose half-life is short, controlled release of drug into the circulation is necessary, to compensate for its rapid elimination. There are a number of drugs and hormones where selectivity of action is enhanced in some way when the agent is given in rate-controlled fashion[1]. Prolongation of drug absorption may be desirable, when, for instance, high rate of absorption would have adverse effects upon the gastro intestinal mucosa and to reduce inter-subject variations in plasma concentration or improve patient compliance. In design of such systems the constraints imposed by the route of administration must be considered.

For oral dosage forms physiological, pathological and pharmacological factors are involved in the control of gastric emptying rate[2]. In addition drug stability in the gastro intestinal tract, concentration and time required to reach site of action require particular attention.

Slow-release oral products can be formulated as single or multiple unit dosage forms. Single unit systems may be erodable or non-disintegrating, both of which are based on matrix forms or dependant upon osmotic pumps. Multiple unit dosage forms have been produced as small pellets each with their own rate-controlling system. The relative merits of the single or pellet preparations have been argued in the pharmaceutical literature and radionuclide labelling of pellet, tablet and osmotic pump systems has revealed that the rates of gastric emptying and small intestinal transit of the three types of formulation are similar[3]. However, solid particles of 5 mm or more in diameter given by mouth may remain in the stomach for prolonged periods.

One of the most important problems in controlled release technology is the development of monolithic (matrix type) polymeric formulations which can release drugs at a constant rate over a prolonged period of time[4].

It has been shown that the fraction of drug release from a matrix with a planar surface or granular composition is linear with the square root of time[5-7]. Drug release from these polymeric matrices fails as a zero-order drug delivery system, because, as the drug is released, the boundary in the matrix at which dissolution occurs recedes from the surface releasing the drug. The problem is one of a decreasing release rate due to an increasing drug diffusion path-length within the matrix (the tortuosity effect).

This paper describes a drug delivery system that under ideal conditions, should release drug at zero-order rate. In this system

there is a constant relationship between the drug diffusion path length and the amount of drug released per unit time.

Higuchi[5], has shown that in the matrix type delivery system the porosity and degree of tortuosity in the capillaries influences the drug release rate. The amount of drug per unit of matrix volume decreases with time as dissolution occurs. Thus if central porosity within a matrix increases to a given fluid environment more drug will dissolve, establishing a constant release rate regardless of tortuosity effect. For such a system we can draw the concentration profile which may exist after the lapse of finite time (figure 1).

In this system release, is generally achieved through a combination of diffusion of active agent and inward diffusion of the environmental fluid. The transport of the active agent is governed by Fick's first law[8].

$$J = \frac{d M_t}{A\, dt} = \frac{-D\, d C_m}{dx}$$

where J is the flux ($g/cm^2/s$), C_m is the concentration of active agent in the polymeric system (g/cm^3), $d C_m/dx$ is the concentration gradient, D is the diffusion coefficient of the active agent in the polymer (cm^2/s), A is the surface area through which diffusion takes place (cm^2), M_t is the mass of agent released, and $d M_t/dt$ is the steady-state release rate at time t.

In the proposed model the amount of drug released remains constant and the amount of drug (Q) in the body following a single dose is given by

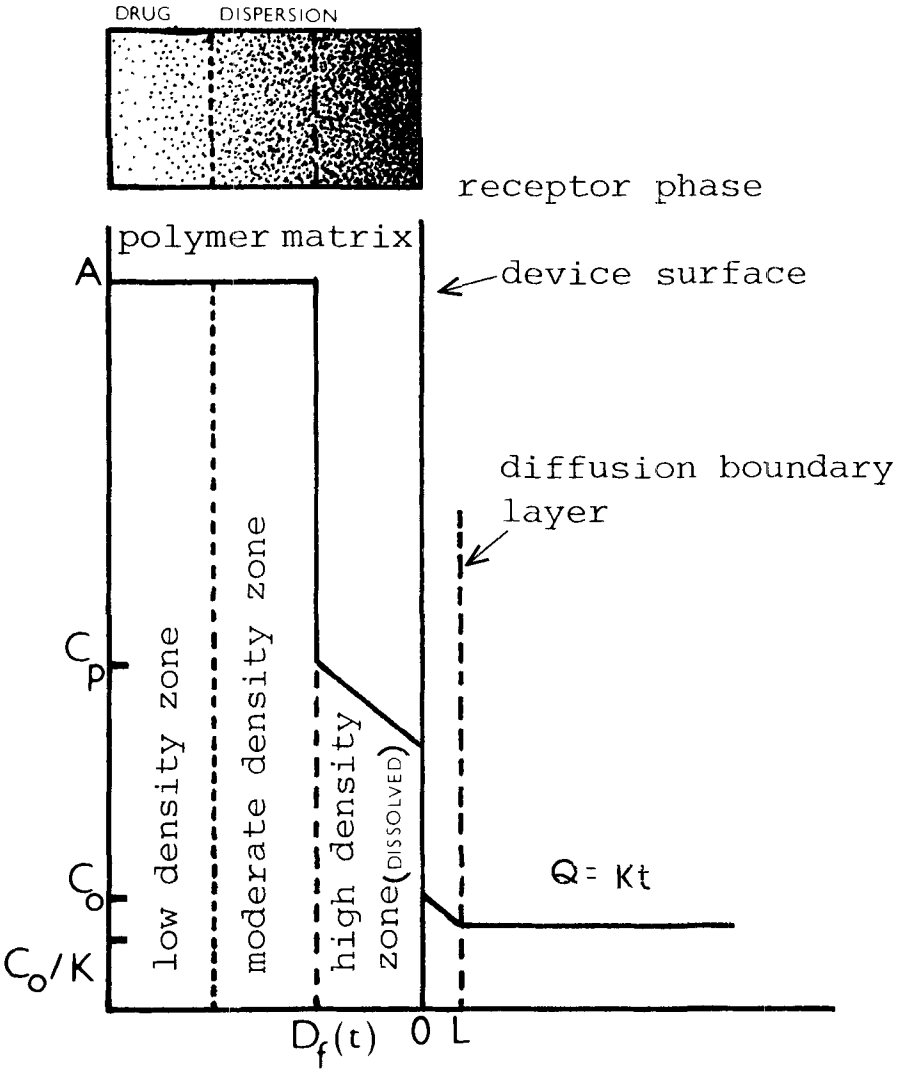

Figure 1

Concentration profile of drug in the polymer matrix (drug loading dose A, saturated drug concentration in the polymer matrix C_p, time dependent drug concentration on the surface of the system C_o, partition coefficient K, dissolution front D_f and diffusion boundary layer L).

the equation [9],

$$Q = \frac{K_o}{VK_{el}} \left[1 - e^{-K_{el}\, t}\right]$$

where K_o is the rate constant governing absorption ($K_o << K_a$) and V is volume of distribution. Drug profiles from this model are influenced by both the rate at which drug is released from the dosage form and also the elimination rate.

In this matrix system there is an instant release from those drug praticles available on the surface and this fast release component should rapidly obtain a desired drug level in the body. This level is then maintained by means of the slow release component. The pharmacokinetics associated with this type of drug release and the amount of drug in the body is given by equation:

$$Q = \frac{D_i K_a}{K_a - K_{el}} \left[e^{-K_{el}t} - e^{-K_a t}\right] + \frac{K_o}{K_{el}} \left[1 - e^{-K_{el}t}\right]$$

where, D_i = instantaneously released drug, K_{el} = first order rate constant for elimination of drug, K_a = first order rate constant for absorption, and K_o = zero-order rate constant for release. The first and second portions of the right hand side of this equation represent the contributions of the fast and slow release components, respectively.

Materials and experimental

Stearyl alcohol and PEG 1000-6000 (BDH-Chemical Ltd., Poole, England), Ethyl cellulose (Hercules Powder Company Limited), Eudragit-retard-BN

70041 and Theophylline crystals commercial grade, lot 1028 and 51647 were used. U.V. spectrophotometer-Perkin Elmer 554 and a manesty tablet machine were used.

Differential scanning calorimetry (DSC)

DSC thermograms were obtained using a Perkin Elmer DSG2 model 3500 data station. Samples of approximately 5 mg were weighed and sealed into aluminium DSC sample pans. Thermograms were measured from 300 to 600°K at a heating rate of 10°K per minute.

Preparation of tablets

To prepare tablets, formulae containing various proportions of theophylline and polymeric composition were used and solid dispersed system was compressed at 80, 110, 150 MN/m^2 as reported previously[10].

Dissolution studies

The in-vitro dissolution rates of the tablets were determined at 37°C using a flow through UV spectrophotometric technique, under sink conditions, at 271 nm with distilled water as dissolution medium. For each determination a tablet was placed in a basket rotated at various speeds and pH values were adjusted so as to simulate the gastro intestinal changes.

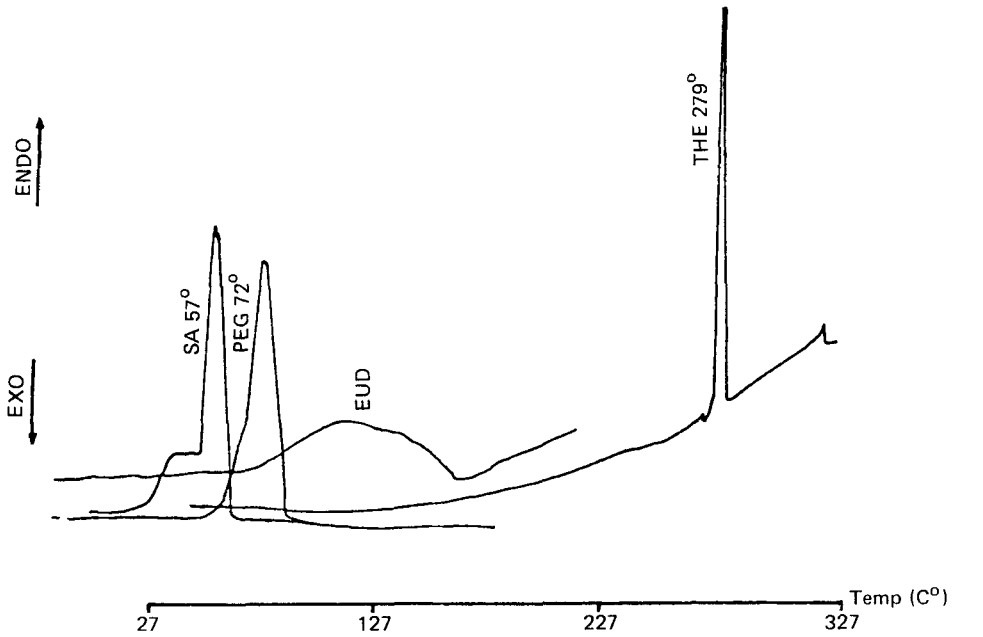

Figure 2
DSC thermograms of various formulation components. SA, PEG, EUD and THE represent stearyl alcohol, polyethylene glycol, eudragite and theophylline base.

RESULTS AND DISCUSSION

DSC thermograms indicated the qualitative composition of the drug formulations and verified the identity of each of the components by their thermal properties. No drug interaction or complexation occured during the manufacturing process (figures 2 and 3). The disappearance of theophylline peaks on scan B figure 3 indicates that complete diffusion of theophylline from the matrix system has occurred. A new peak at temperature range of 90 to 100°C on scan B indicates that part of polymeric composition has been dissolved during the diffusion process.

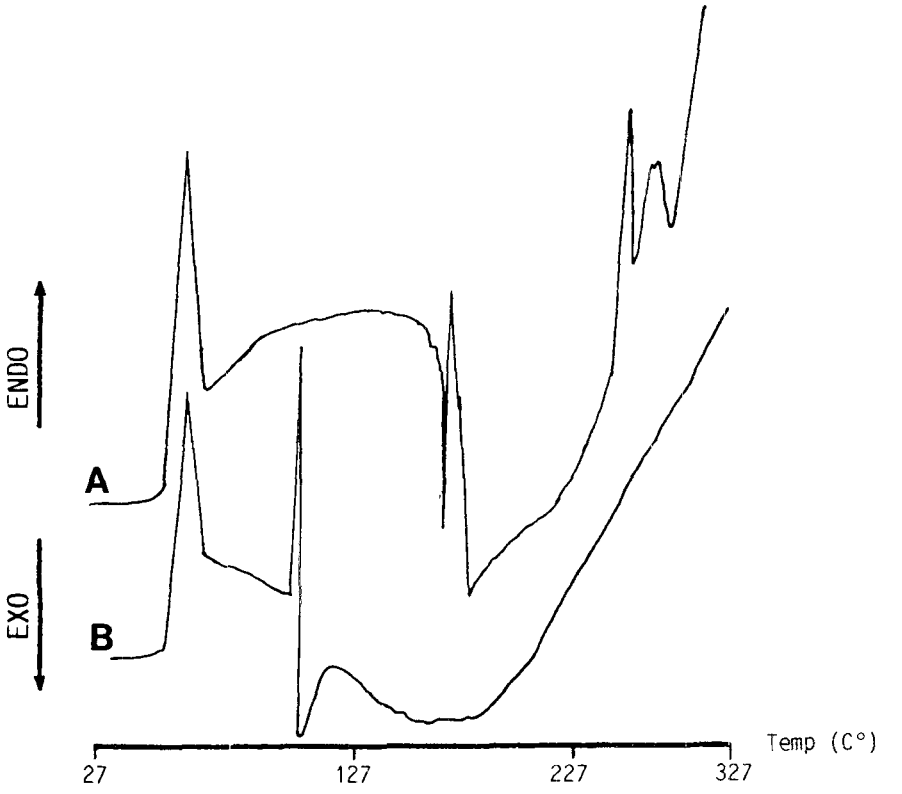

Figure 3
DSC thermograms of theophylline tablet formulation (A) and after complete diffusion of theophylline from the polymeric matrix (B).

Figure 4 reveals that the release rate is independent of stirring speed, under sink conditions and the variations of delivery rates were not significant. In addition, reproducibility of the release profiles indicated that polymer matrices produced were essentially isotropic with respect to drug content and drug release. This suggests that there is no significant drug migration during the manufacturing process. Relative Standard deviations of release rates were within

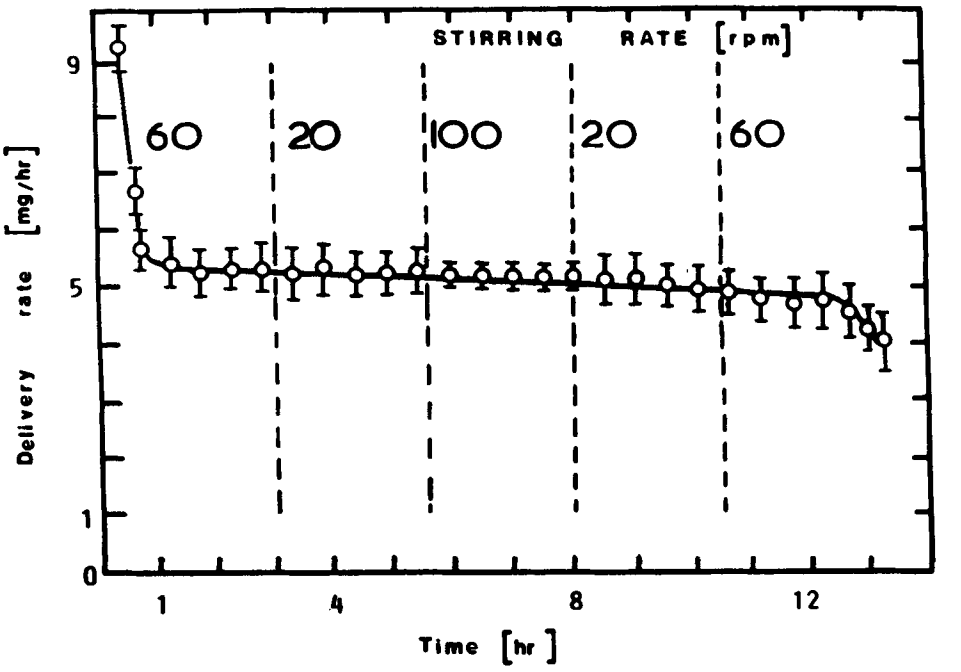

Figure 4
Reproducibility and in vitro release rates for 10 theophylline tablets at various stirring speed vs. time from polymeric matrix system.

10-15% of the respective means with the exception of the early release period.

Figure 5 illustrates the effect of pH versus stirring speed versus time on drug delivery rate in a three dimensional display and indicates a zero-order delivery rate.

This design results in a heterogeneous, polymeric, matrix system which being of low density floats, and releases drug by a diffusion

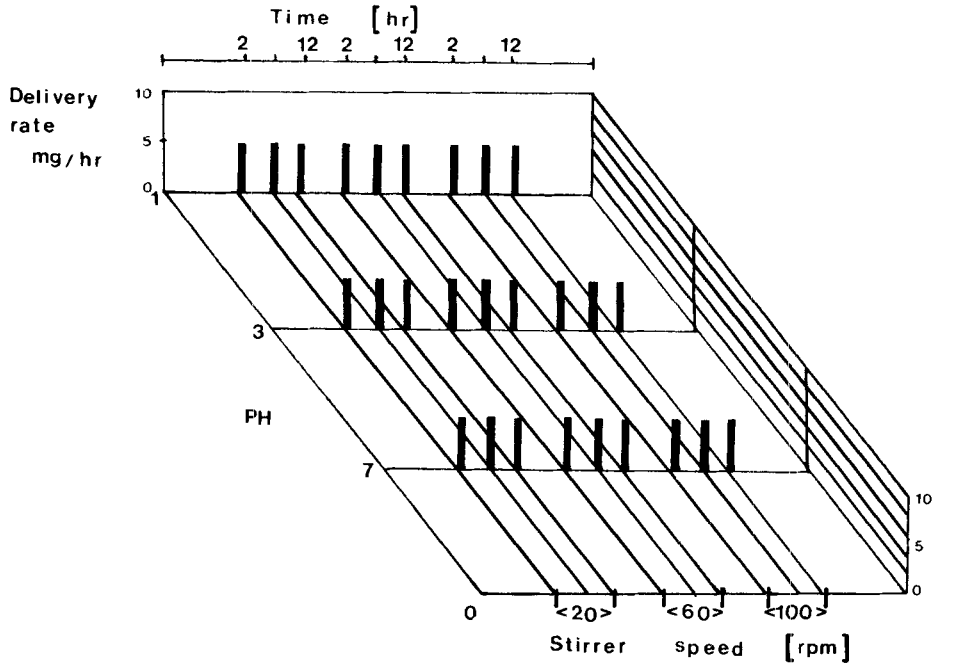

Figure 5
The effect of pH vs. stirrer speed vs. time on drug delivery rate in a three dimensional display which indicates the zero-order delivery rate.

mechanism. Figure 6 demonstrates the in-vitro diffusion of a dye from the floating polymeric system, simulating drug release.

These results indicate the importance of density and degree of porosity together with the manufacturing procedure used in producing heterogeneous polymeric systems. It may be difficult to incorporate drugs and achieve the differential density zones required, on the other hand uniform density may cause a release period linear with respect to the square root of time. There appeared to be three release phases.

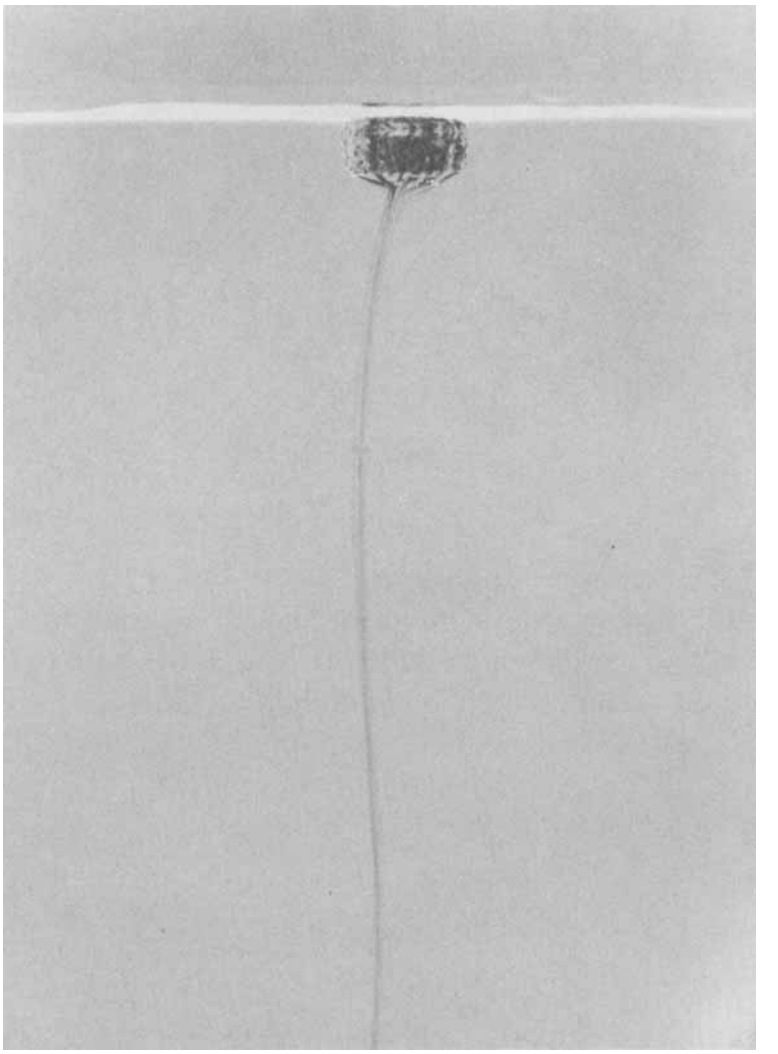

Figure 6
In vitro diffusion from the floating polymeric system in which a dye simulates the drug.

(i) an initial period of rapid release,

(ii) a period when release is linear with respect to time,

and (iii) a final period when release tapers off.

Further work is in progress to establish these mechanisms and investigate in-vivo correlations.

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