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COMMUNICATION

The Use of a Hydrophobic Matrix for the Sustained Release of a Highly Water Soluble Drug

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ABSTRACT

An experimental investigation into the use of a hydrophobic matrix to control the release of a highly water soluble drug was undertaken. Matrices consisting of hydrogenated vegetable oil and calcium sulfate with a 4% drug loading showed a sustained-release profile of up to 24 hr. The release mechanism from such matrices seemed to obey both root time kinetics and first-order behavior. Investigations showed that the effect of geometry had a significant effect on the drug release rate.
Key Words: *Controlled release; Geometry; Hydrophobic matrix; Release rate; Shape.*

INTRODUCTION

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959 (1) and was the focus of much attention, leading to the development of the Duretter™ (A. B. Hassle, Lund, Sweden) and Gradumet™ (Abbot, Chicago, IL) technologies (2,3). In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has to diffuse through a network of channels that exist between compacted polymer particles (4).

Examples of materials that have been used as inert or hydrophobic matrices include polyvinylchloride, polyethylene, ethylcellulose, and the methylacrylate polymers and their copolymers (4). Few studies on the use of Lubritab™ (Mendell, New York) (hydrogenated vegetable oil) and Compactrol™ (Mendell, New York) (calcium sulfate) as matrix-forming materials exist in the litera-

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ture. In this work, a highly water soluble compound was used, with a view of producing a 24-hr oral controlled-release dosage form. Investigations into the effects of geometry on drug release were also initiated.

MATERIALS AND METHODS

Materials

Hydrogenated vegetable oil (Lubritab) and calcium sulfate (Compactrol) were received from Edward Mendell and Company (New York). Magnesium stearate was received from Akros Chemicals (Venlo, Holland). The drug substance used in these studies has a high water solubility (>100 mg/ml) and a molecular weight of about 300 (supplied by Smithkline Beecham Pharmaceuticals, Cork, Ireland).

Tablet Preparation

Tablet formulations were prepared in the following manner. Drug (4%) was mixed with Lubritab (60%) and Compactrol (35%) for 10 min using a cube blender. Magnesium stearate (1%) was then added, and the blend was then remixed for a further 2 min. The formulation was compressed into tablets (200 ± 10 mg) using a Manesty single-punch F-press machine (Liverpool, UK) (10 mm punch and die) with tablet hardnesses of approximately 5 kPa.

To investigate the effects of different geometries and surface areas on drug release from inert matrix systems, different shape tablets were produced on the Manesty F-press machine. The geometries investigated were thin cylindrical compacts and quasi-spherical tablets (manufactured using deep concave punches).

Dissolution Testing: USP Apparatus 2

The controlled-release formulation was tested using a USP 2 rotating paddle dissolution apparatus (Hanson Research, Chatsworth, USA). The dosage form was placed into gold-coated baskets before immersion into 900 ml of deaerated Tris-maleate buffer pH 7.0 at 37.5°C. The gold-coated baskets were used to prevent the dosage forms from floating to the surface. The media was agitated by paddles stirring at 50 rpm. Samples of 100 µl of dissolution media were removed for analysis by high-peformance liquid chromatography (HPLC) at hourly intervals.

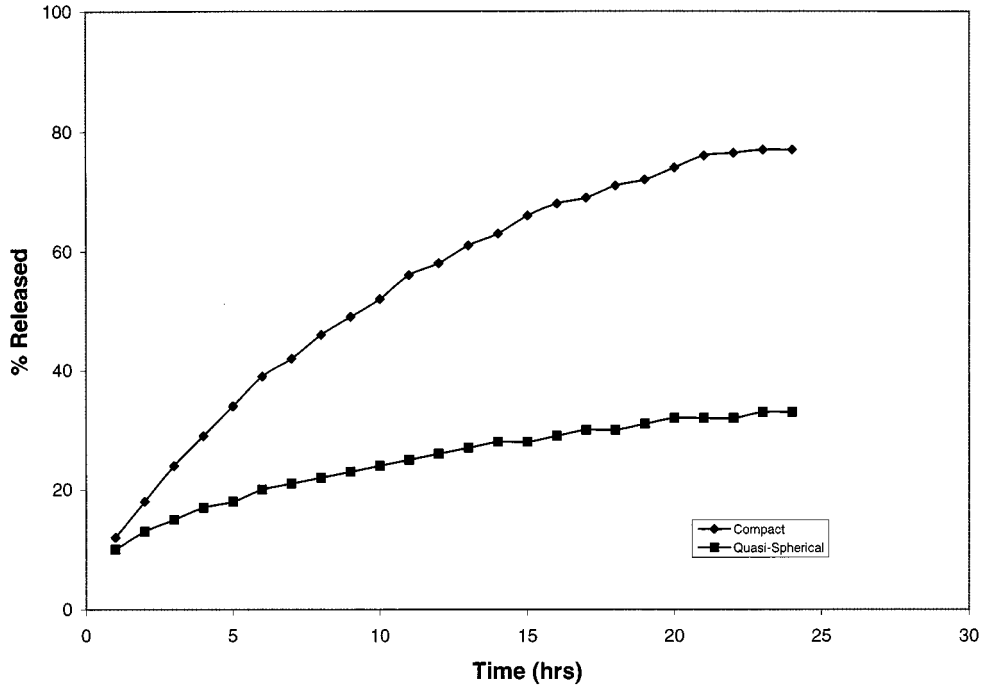

Figure 1. A plot of the percentage drug released versus time for the different geometries using the USP 2 dissolution apparatus.

Analytical Methods

A reversed-phase, isocratic HPLC method was used to determine the percentage of drug substance present in the dissolution samples. The samples were injected directly onto a Kromasil C8 15cm column (Hichrom, Reading, UK) at room temperature and the ultraviolet (UV) detector was set at 250 nm.

RESULTS

Figure 1 shows the percentage of drug released as a function of time for the compact and spherically shape tablets. However, it can be seen that, with respect to time, the release profile for both dosage forms are nonlinear, but vary markedly with shape. Simoons (5) was the first to try to relate the rate of release of drugs from matrix tablets using Fick's first law of diffusion. Higuchi (6) proposed an equation to predict release rates from a planar surface of a system in which the drug particles are incorporated in a granular matrix and released by the leaching action of the eluting fluid:

$$Q = [D\varepsilon/\tau C_c t(2A - \varepsilon C_s)]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area of surface at time t, D is the diffusion coefficient of drug in the eluting fluid, ε is the porosity of the leached part of the matrix, C_c is the solubility of the drug in the eluting fluid, A is the concentration of drug/unit volume of matrix, and τ is the tortuosity of the matrix The equation predicts that the amount of drug released will be directly proportional to the square root of time. This equation assumes that the drug particles are small relative to the average distance of diffusion and are uniformly distributed within the matrix.

For the dosage forms to obey Higuchi kinetics, a linear relationship should exist with root time. In Fig. 2, the percentage drug released for both geometries is plotted as a function of root time, and a reasonable correlation was obtained (refer to Table 1). However, the Higuchi model does not adequately explain the marked impact that the shape seems to have on the release profile.

Recent work (7) with inert matrices of dicalcium phosphate dihydrate also showed that Higuchi kinetics were not satisfactory in explaining the release mechanisms

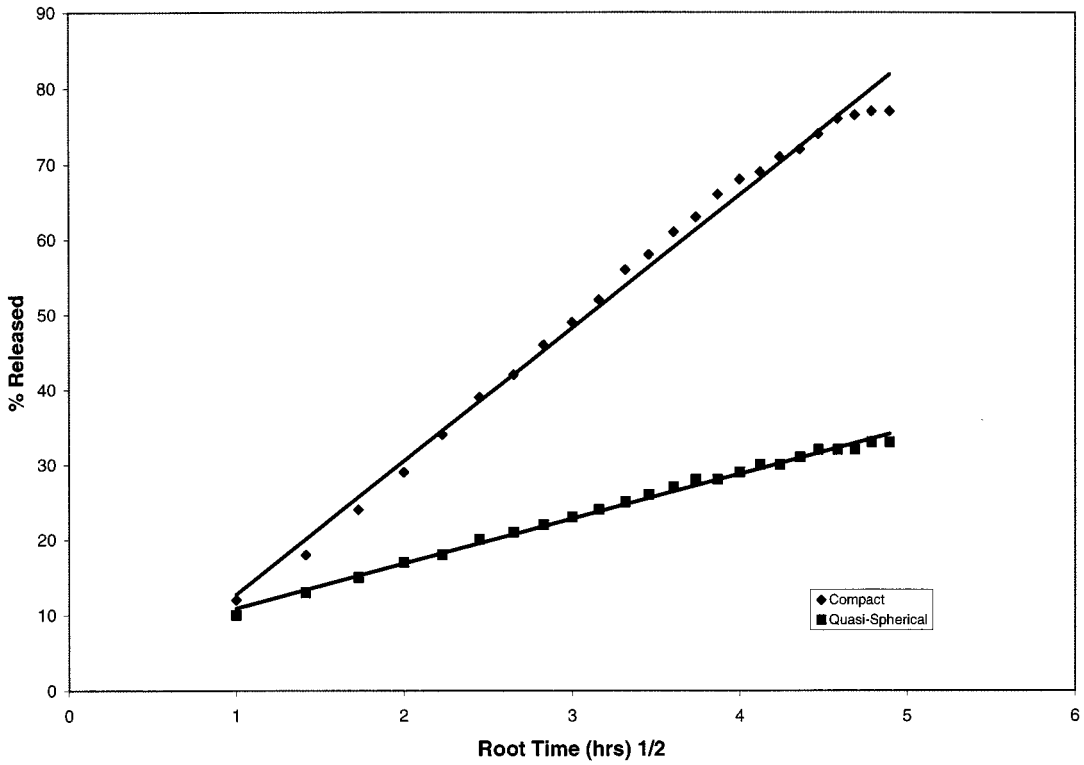

Figure 2. A plot of the percentage drug released versus root time for the different geometries using the USP 2 dissolution apparatus.

Table 1

Experimentally Determined Correlation Coefficients

Shape	Root Time Fit	First-Order Fit	K
Compact	0.992	0.993	0.550
Quasi-spherical	0.994	0.998	0.380

from inert matrices with low drug loadings. Therefore, these workers devised a simple model to explain the release of highly water soluble drugs from inert, insoluble, nonswelling porous matrices. According to this model, the release of drug from such systems can be explained using a first-order kinetic expression as follows:

$$Q = Q_o e^{-Kt} \tag{2}$$

where Q is the amount released, Q_o is the initial amount, t is time, and K is a rate constant. A release profile that obeys first-order kinetics will have a release rate (dQ/dt) at any given time that is directly proportional to the drug concentration and a rate constant that is independent of the initial drug concentration. In this model, the rate constant is related to the geometry of the matrix as follows:

$$\text{General expression} \qquad K = K_d \times A/V \tag{3}$$

where K_d is a diffusion-related proportionality constant, A is the void area, and V is the void volume. The model assumes that the matrix is insoluble and does not swell, that the drug is also highly water soluble, and that the void volume of the matrix is sufficient for complete dissolution of the drug. The model also assumes that the ratio of surface area to the volume of the tablet is represented by the ratio of the void area to void volume. Thus, Eq. 3 implies a linear relationship between the rate constant K and the surface area of the tablet expressed as area per unit volume. Therefore, if the ratio of the surface area to volume for one dosage form is greater then that for another, then the release rate of drug from that dosage form should be greater.

For a circular cylinder of radius r and height h, the rate constant will be a linear function of the reciprocal

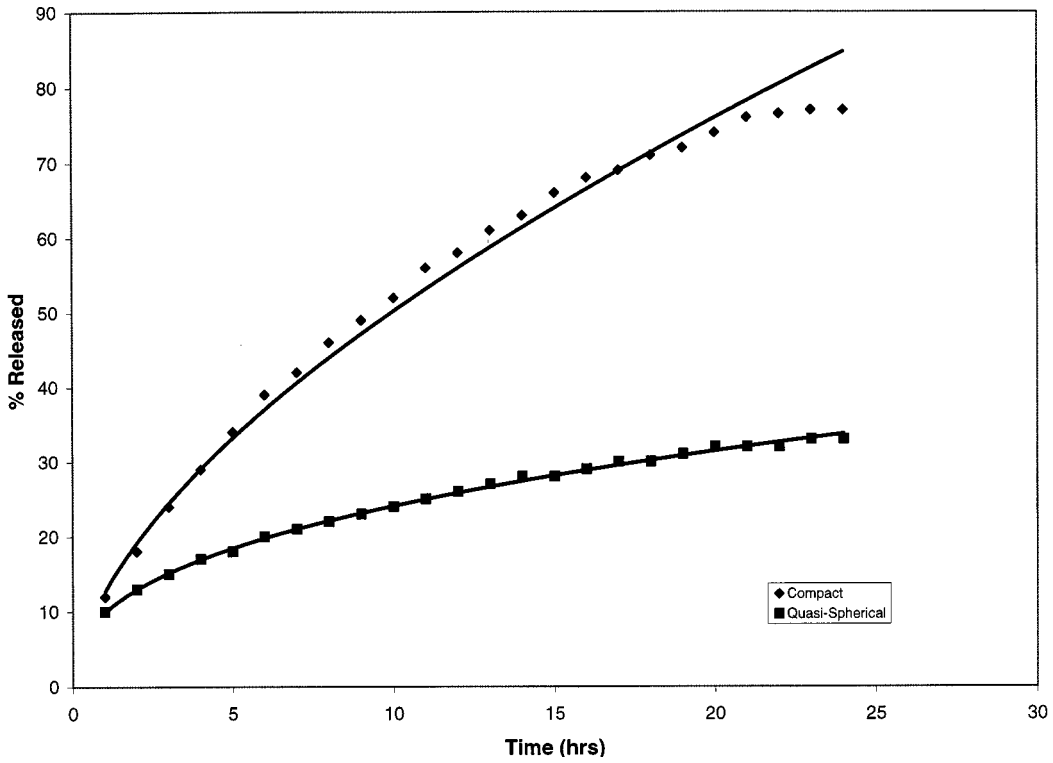

Figure 3. A plot, fitted to Eq. 2, of the percentage drug released versus time for the different geometries using the USP 2 dissolution apparatus.

Thin Compact Quasi-Spherical

A/V ~ 18 A/V ~ 13

Structure 1.

of the height when the radius of the matrix is held constant and vice versa; therefore, one can write

$$K = K_d 2(1/r + 1/h) \quad (4)$$

For a sphere, the rate constant will be inversely proportional to the radius. The geometries investigated were a thin cylindrical compact and a quasi-spherical shape as in Structure 1. Approximate values for the ratios of surface area to volume (A/V) were calculated for the various geometries. The A/V ratio calculated for the quasi-spherical tablet is slightly higher then it should be since a true sphere would have an A/V ratio of 12. According to Eq. 3, the release rate from the compact should be greater then that for the quasi-spherical shape by approximately 1.4 times. Figure 3 reveals the release profiles from both dosage forms fitted according to Eq. 2. The fitting data and values for the rate constant are also shown in Table 1. In both cases, a slightly better correlation was observed with the first-order model compared to the Higuchi root model. In addition, it can be seen that the ratio between the rate constant *K* for the compact matrix compared to that obtained for the quasi-spherical shape is about 1.4, which compares favorably with the differences in the ratios of surface area to volume for both geometries.

In conclusion, these results seem to show that inert matrices of differing geometries may produce different drug release profiles. Further work is needed to investigate this phenomenon in greater detail.

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