Pharmaceutical Research, Vol. 7, No. 11, 1990

Technical Note

A Flat Circular Hole Device for Zero-Order Release of Drugs: Characterization of the Moving Dissolution Boundary

Dinesh S. Mishra[1] and Samuel H. Yalkowsky[1,2]

Received July 18, 1989; accepted April 23, 1990

KEY WORDS: zero-order release; hemisphere; diffusion controlled matrix release; progesterone; dissolution boundary; drug delivery.

INTRODUCTION

The present study experimentally evaluates the moving dissolution boundary in a flat circular hole matrix device. The results demonstrate that a flat circular hole device produces a hemispherical receding dissolution front and would be expected to approximate zero-order release profiles for drugs. Release of a model drug, progesterone, is shown to be approximately zero order.

Diffusion-controlled matrix devices have received attention for controlled delivery of drugs (6). These devices containing suspended drug normally give release rates proportional to the square root of time (2,5). This is due to the release rate being inversely proportional to the distance that the drug must travel from within the matrix to the surface. Since the distance increases with time the release rate decreases.

Zero-order release from matrix systems can be achieved by varying the matrix geometry (1,3,4,7). The idea behind the geometric approach is to increase the surface area of drug dissolution as the diffusional distance increases. The increasing distance the drug must travel is offset by increasing the effective area over which the drug dissolution takes place.

Rhine *et al.* (7) showed that a hemispherical device with a hemispherical hole gives a zero-order release. This device, however, is difficult to fabricate and is not feasible to manufacture on a large scale. Kuu and Yalkowsky (3) described a zero-order device in a much simpler geometry, the rectangular matrix. However, this device also requires hemispherical holes, which may be difficult to manufacture.

In this work we describe a device with rectangular geometry with a flat circular hole through which the drug is released. The objective of this study is to characterize the moving drug dissolution boundary in the flat circular hole device compared to the simple rectangular matrix device.

[1] Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721.

[2] To whom correspondence should be addressed.

MATERIALS AND METHODS

Silicone Matrix

Silicone matrices containing progesterone are made in the following way: progesterone is suspended in polydimethylsiloxane fluid (350-cs viscosity) and then mixed with Silastic MDX-4-4210. The curing agent is then added and mixed thoroughly to obtain an even distribution of drug particles. The mixture is then placed in Teflon molds which are placed in a closed chamber and the pressure is reduced until all the entrapped air is removed. The device is then placed in an oven at 50°C for 1 hr. The amounts of the ingredients used are as follows: progesterone, 4% (w/w); polydimethylsiloxane fluid, 5% (w/w); Silastic MDX-4-4210, 90% (w/w); and catalyst, 5% (w/w).

Flat Circular Hole Device

The flat circular hole device is fabricated using the silicone matrix described above. An aluminum sheet is layered with pressure-sensitive adhesive (Dow Corning 281) and mixed with the curing agent. The adhesive is allowed to cure for 1 hr. Holes (0.3-cm diameter) are punched into the sheet with a hole puncher. The aluminum sheet is then layered onto the planar device (2 cm × 2 cm) which was made earlier with the hole in the center. The planar device is also layered on all sides except one to make the rectangular device, with

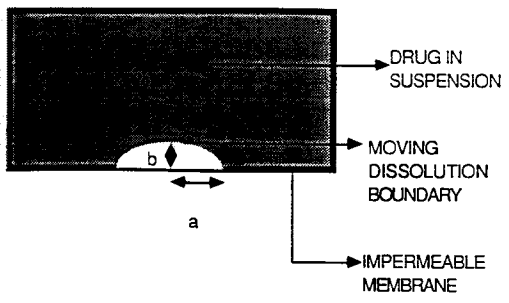

Fig. 1. Schematic diagram of the flat circular hole device.

0724-8741/90/1100-1195$06.00/0

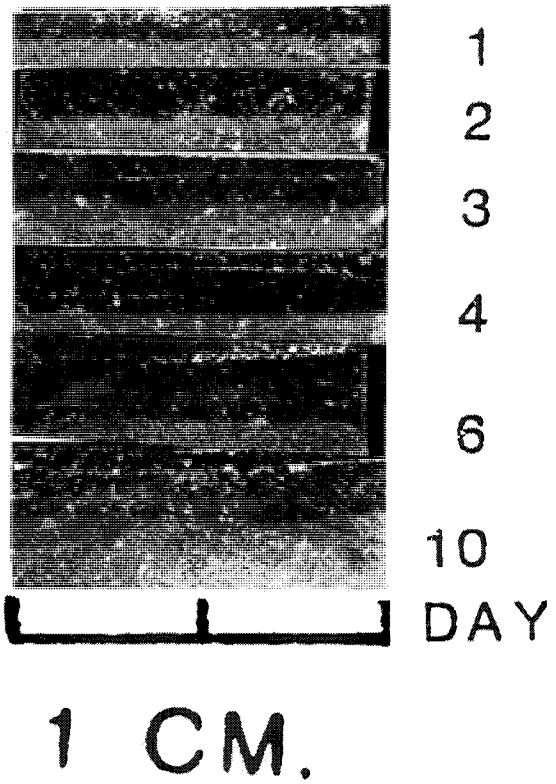

Fig. 2. Photograph of receding layer in the rectangular device with one releasing surface.

one releasing surface used for comparison. Figure 1 shows the schematic diagram of the flat hole device.

Release Study

The devices are placed in 20-ml scintillation vials with 15 ml of aqueous solution containing polyethylene glycol 400 (20%) and methanol (10%). The solution is removed periodically and replaced with fresh solution. The solution is then analyzed for progesterone on a Beckmann DU-8 spectrophotometer at 240 nm. For the characterization of the moving dissolution boundary the devices are taken out after a period of time. Cross sections of the device are taken through the hole and photographed on a high-contrast film.

RESULTS AND DISCUSSION

Figures 2 and 3 show the photographs of the moving dissolution boundary for both the planar and the flat hole device. The photographs of the planar device (one dimensional) is taken for comparison. It can be seen from Figure 2 that the dissolution boundary changes its shape from being flat to nearly hemispherical with time.

To evaluate the flat circular hole leading to a hemispherical receding dissolution boundary, we define the ratio b/a (refer to Fig. 1). At the start of the experiment $b = 0$ and the ratio is zero. However, with the increase in time, b increases much faster than a, and the ratio b/a asymptotically approaches unity. The dissolution boundary will be perfectly hemispherical when the ratio is unity. The ratio b/a is plotted against time in Fig. 4. The flat circular hole device reaches a value of 0.8 in about 10 days.

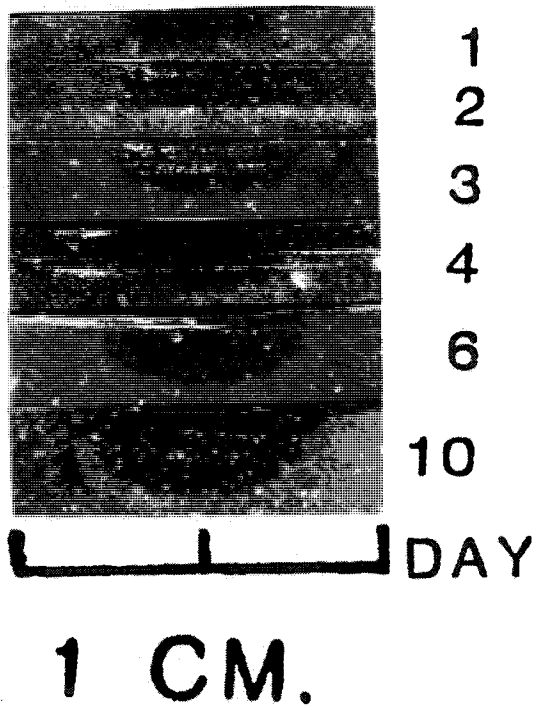

Fig. 3. Photograph of the receding layer in the flat circular hole device.

The time to achieve nearly hemispherical dissolution boundary can be decreased by decreasing the radius of the flat circular hole (a at time zero). The lower the value of a, the faster the hemispherical dissolution boundary is established. However, this reduces the rate of drug release from the device. This can be remedied by using the multiple-hole concept of Kuu and Yalkowsky (3). The amount of drug released from the multiple-hole device will be proportional to the total surface area over which the drug is released. By using the multiple-hole device, the individual hole size (a) can be reduced, keeping the total surface area for the drug release much higher.

In the rectangular device with the width much larger than the radius of the hole (a), the device will approximate zero-order release until the hemispherical dissolution bound-

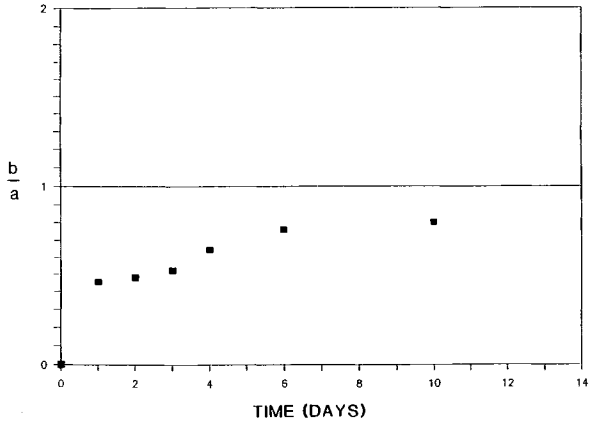

Fig. 4. Plot of b/a as a function of time for the flat circular hole device.

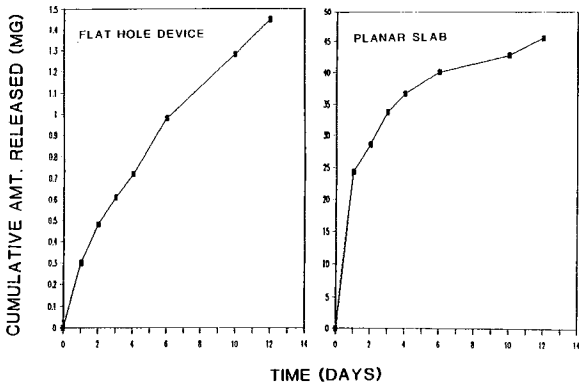

Fig. 5. Plot of cumulative amount released as a function of time for (a) flat circular hole device and (b) rectangular device.

ary ceases to exist. As the radius of the hemisphere (*b*) increases the hemisphere will collapse due to the intersection with the device, or with other holes in the case of the multiple-hole device. The time of the zero-order release can be maximized by using multiple holes on both sides of the device as well as decreasing the individual hole size (3).

The release of the model drug, progesterone, in the flat circular hole device as well as the planar matrix was performed. In Fig. 5 the cumulative release of progesterone is plotted against time for both the flat hole and the planar device. It is clear that the flat hole device gives release profiles very close to zero order after a period of 3 days. This result is encouraging since a nearly hemispherical dissolution boundary is only achieved in 10 days, but the device approximates zero-order release after a period of only 3 days. The photographs reveal that in 3 days the dissolution boundary has a significant curvature and thereafter the area of drug dissolution increases.

CONCLUSIONS

This study shows that the flat circular hole closely approximates a zero-order delivery of a model drug. The moving drug dissolution boundary is shown to approach a hemisphere with time. The study also shows that it is possible to achieve a zero-order delivery of drugs from a rectangular matrix without resorting to exotic geometric shapes.

REFERENCES

1. D. Brooke and R. J. Washkuhn. *J. Pharm. Sci.* 66:159 (1977).
2. T. Higuchi. *J. Pharm. Sci.* 52:1145 (1963).
3. W. Y. Kuu and S. H. Yalkowsky. *J. Pharm. Sci.* 74:926 (1985).
4. R. A. Lipper and W. I. Higuchi. *J. Pharm. Sci.* 66:163 (1977).
5. D. R. Paul and S. K. McSpadden. *J. Membr. Sci.* 1:33 (1976).
6. J. R. Robinson and V. H. L. Lee. *Controlled Drug Delivery: Fundamentals and Applications,* 2nd ed., Marcel Dekker, New York, 1987.
7. W. Rhine, V. Sukhatme, D. S. T. Hsieh, and R. S. Langer. A new approach to achieve zero order release kinetics from diffusion controlled polymer matrix systems. In R. Baker (ed.), *Controlled Release of Bioactive Agents,* Academic Press, New York, 1980.