DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(15), 2041-2054 (1991)

LATEX FILM MATRIX SYSTEMS WITH A CONCENTRATION GRADIENT FOR CONTROLLED DRUG DELIVERY

Luk Chiu Li[1]* and Yu-Hsing Tu[2]

University of Oklahoma
College of Pharmacy
1110 N. Stonewall
P.O. Box 26901
Oklahoma City, Oklahoma 73190

ABSTRACT

Latex film matrix systems with a nonuniform drug distribution were prepared by a coating process. In this process a drug concentration gradient in the coating dispersion was generated by the programmable pumping of the latex into a drug reservoir which contained the drug and latex. The film matrix formed by the dispersion would have a built-in drug concentration gradient as the coating process proceeded. A mathematical model was developed to describe the concentration change of the active ingredient in the coating dispersion as a function of the

* Correspondence
Present Address:

[1] Hospital Products Division, Abbott Laboratories, Abbott Park, IL 60064-3500.
[2] Fisons Pharmaceuticals, P.O. Box 1710, Rochester, NY 14623.

spraying rate of the coating dispersion, the pumping rate of the latex into the drug reservoir, and the initial drug concentration in the dispersion. The applicability of this process was demonstrated by the controlled in vitro dissolution of acetaminophen from ethylcellulose latex film matrices formed on glass beads. The release profile of the active ingredient from the systems changed as the drug concentration gradient profile in the matrix was altered, and a higher drug concentration gradient in the matrix resulted in a slower release rate and a more linear release profile. A faster drug release rate can also be achieved by incorporating a highly water soluble ingredient in the concentration gradient matrix.

INTRODUCTION

The concept of controlled drug delivery for improved drug therapy has generated broad research interests in pharmaceutical sciences during the last two decades. Diffusion-controlled drug delivery systems which involve the use of polymeric ingredients have generally been classified into two categories: reservoir or membrane devices and monolithic or matrix devices. The rate versus time profiles for drug release from membrane systems are constant as long as the reservoir is saturated with the active ingredient. Although the constant drug release profile is highly desirable to achieve a uniform therapeutic drug effect, the membrane devices have several disadvantages, such as their relatively high manufacturing cost and the danger of dose dumping if membrane integrity is not maintained. Matrix-type drug delivery devices consist of homogenous dispersion of an

active ingredient in a polymeric base. Matrix devices generally require fewer steps to prepare and are less expensive as compared to the membrane systems, but the delivery of active ingredients from polymer matrices is characterized by an exponential decay of the release rate over time. The use of non-uniform concentration distribution has been explored as a mechanism to achieve constant drug release from matrix devices. In 1981, Bogentoft and Appelgren (1) patented the preparation of granules, with decreasing concentration of active ingredient from the core to the outer layer of the granules, using a conventional pan or air suspending coating method. Later, Lee (2) reported a novel method to achieve a constant rate of drug release from glassy hydrogel beads via an immobilized non-uniform drug concentration distribution. In recent years, the use of a film coating process in preparing matrix systems with a non-uniform drug distribution has generated new research interest in pharmaceutical sciences (3-5). The coating process reported by these investigators involved a step-wise concentration change of the active ingredient in the coating solution. Therefore, matrix systems were formed with layers having a step-wise change in concentration of the active ingredient. The release of the active ingredient from such a system may exhibit a step-wise profile. This paper presents the design of a film coating process which would generate a latex film matrix system with a continuous drug concentration gradient. The influence of the process parameters in this process on the concentration profile of the active ingredient in the matrix system is defined using a mathematical model.

The relationship between the drug concentration profile and its release profile from the matrix can then be established. This semi-empirical approach allows the modification of the process parameters so that a polymer film matrix with the desired zero-order controlled release of the active ingredient can be prepared.

EXPERIMENTAL

Materials

Acetaminophen (APAP) was USP grade and provided by Mallinckrodt Company (St. Louis, MO). Surelease®, an ethylcellulose latex, was supplied by Colorcon Incorporation (West Point, PA). Sucrose was pharmaceutical grade and provided by Amstar Sugar Corporation (New York, NY).

Methods

Design of the Coating Process

The concentration gradient of the drug in the coating dispersion is generated using the following model.

$$L \xrightarrow{k_i} D \xrightarrow{k_o} \text{Coater}$$

L represents the latex reservoir and D represents the drug reservoir. The latex is pumped into the drug reservoir via a peristaltic pump at the rate of k_i and the dispersion in the drug reservoir is applied to the cores in the coater at the rate of k_o. The rate k_o is larger than k_i so that the content of the drug reservoir will be exhausted at the end of the coating.

The rate of change in the volume of the drug reservoir (V) can be described as follows:

$$dV/dt = k_i - k_o \quad (1)$$

The change in volume with time is obtained by integration of Eq. 1 between time = 0 and time = t.

$$V = V_o + (k_i - k_o)\, t \quad (2)$$

The change of the amount of drug in the drug reservoir (D) with time is described by the following expression:

$$dVC/dt = -k_o C \quad (3)$$

where C is the drug concentration in the drug reservoir at time t. Substituting Eq. 2 into Eq. 3 gives:

$$d[V_o + (k_i - k_o)t]C/dt = -k_o C \quad (4)$$

Differentiating Eq. 4 gives:

$$[V_o + (k_i - k_o)t]dC/dt = -k_i C \quad (5)$$

and

$$dC/dt = -k_i C/[V_o + (k_i - k_o)t] \quad (6)$$

Integrating Eq. 6 between time = 0 and time = t gives:

$$C = C_o\,[1 + (k_i - k_o)t/V_o]^{[ki/(ko-ki)]} \quad (7)$$

Assuming the latex solid concentration in both drug reservoir and latex reservoir is C_l, the percent of drug in the latex (calculated as solid) in the coating dispersion at time t can be calculated as follows:

$$P = [C/(C_l + C)] \times 100\% \quad (8)$$

The instant mixing of the latex pumped from the latex reservoir into the drug reservoir generates a continuous drug concentration change

in the coating dispersion, which represents the concentration profile of the drug in the latex film matrix produced by the coating process. Therefore, by changing the various parameters in the model, different concentration profiles of the drug in the matrix can be achieved.

In this study a 6-inch Unit Glatt coating column was used as the coater. Thirty grams of glass beads (4.5 mm in diameter), which were used as the core for coating were mixed with 1.5 Kg of lactose tablets (1/4 inch in diameter) in the coating column. Four different coating operations were carried out by varying C_o, k_i and V_o to yield four different drug concentration gradients. The total amount of latex (solid) and drug used in all four coatings was equal to 100 g respectively. In spite of the difference in concentration gradient, the total amount of latex and drug in the matrix maintains a 1 to 1 ratio for all four systems. The process parameters for the coating operation are shown in Table 1. In each coating operation the time taken for the drug reservoir to exhaust is calculated by dividing the initial volume of the drug reservoir, V_o by the difference between k_o and k_i. Using the rates listed in Table 1, all coating runs were completed in 133.3 minutes and the total volume of coating dispersion and latex applied was equal to 2 liters.

The effect of incorporating sucrose, a highly water soluble ingredient, in the matrix on the in vitro release profile of acetaminophen was also studied. Three different levels of sucrose (10%, 15% and 20% of the total weight of the matrix) were added to the film matrix system SIM-4. The total amounts of sucrose were divided in half and added to

Table 1. The Process Parameters for the Coating Operation.

Film Matrix System	V_o (ml)	C_o* (%, w/v)	k_o (ml/min)	k_i (ml/min)
SIM-1	2,000	5.0	15.0	0.0
SIM-2	1,333	7.5	15.0	5.0
SIM-3	1,000	10.0	15.0	7.5
SIM-4	667	15.0	15.0	10.0

* In both the drug reservoir and polymer reservoir, the content of Surelease® solid was kept at a 5% level.

the latex reservoir and drug reservoir to yield the same sucrose concentration in both reservoirs.

Determination of the Drug Content in Coated Latex Film Matrix

The film matrix was dissolved from the coated glass beads in 95% alcohol. The ethylcellulose and other additives in Surelease® did not show any UV absorption in the ethanol solution. The amount of acetaminophen in the solid film matrix was determined by measuring the UV absorbance of the alcohol solution at a wavelength of 248 nm. The weight of the coating on the glass bead was taken as the difference in weight of the bead before and after the dissolution of the matrix in alcohol. The percent of acetaminophen in the film matrix was subsequently calculated.

Determination of the Drug Release from Latex Film Matrix

The in vitro release profiles of acetaminophen from the coated beads were determined using the standard USP Dissolution Method I (the basket method). The apparatus used was a six-unit dissolution tester (Vanderkamp 600). The dissolution medium was degassed USP Simulated Gastric Fluid (without pepsin). The dissolution medium was circulated through a UV spectrophotometer (Perkin-Elmer Lambda 38) which was interfaced with the Lambda 3 Data Station equipped with the Perkin-Elmer PR-100 Printer. The absorbance of the dissolution medium was measured and recorded at different time intervals. The amount of acetaminophen released was calculated by means of a calibration curve. The plot of the cumulative percent released against time elapsed gave the drug release profile.

RESULTS AND DISCUSSION

Using the process parameters listed in Table 1, the percent of acetaminophen in the total solids of the coating dispersions used in the four different coating operations, was calculated as a function of time using Equations 7 and 8. The concentration-time profiles are presented in Figure 1. When the coating dispersion with a constant drug concentration was used, a uniform distribution of acetaminophen was produced in the latex matrix and the concentration-time profile for this system was a horizontal straight line (SM1). Depending on the ratio of the pumping rate of the latex into the drug reservoir (k_i) and the spraying rate of the dispersion into the coater (k_o), three distinctly different gradient profiles

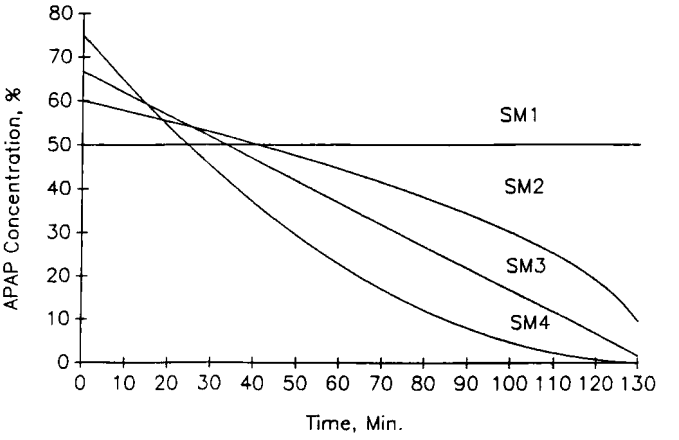

FIGURE 1

The four concentration-time profiles of acetaminophen in coating dispersions computed using the processing parameters listed in Table 1.

were generated. With a 1 to 3 ratio (k_i/k_o), a convex curve profile (SM2) was obtained. When k_i was equal to half of k_o, the exponent term in Equation 7 was equal to one and the gradient profile (SM3) was linear. A concave curve profile (SM4) was obtained when k_i was two third of k_o. Since the film matrix was formed by a continuous layering process, the distribution of acetaminophen in the latex film matrix would exhibit similar gradient profiles as the coating dispersion (Figure 1), and the time axis actually represents the distance from the surface of the glass bead to the surface of the film matrix. For the matrix systems with sucrose added, the percent of APAP in the film matrix was reduced because of the presence of sucrose, but the relative percentage of APAP and Surelease® solid still stayed the same as depicted by the profile (SIM-4) in Figure 1.

Table 2. The Weight of Latex Film and the Percent of Acetaminophen in the Film on the Coated Glass Beads.

Film Matrix System	Latex Film (mg)*	% Acetaminophen (w/w)*
SIM-1	7.5	51.4
	(0.62)	(1.29)
SIM-2	7.5	49.8
	(0.59)	(1.97)
SIM-3	7.2	50.3
	(0.55)	(2.44)
SIM-4	7.7	50.3
	(0.61)	(1.82)

* Mean and standard deviation for five coated glass beads.

Table 2 shows the weight of latex film coated on the glass beads and the percent of acetaminophen in the solid film. A high degree of uniformity in both film weight and percent of acetaminophen in the film matrix are shown for the four systems with different concentration gradients. Furthermore, the total amount of acetaminophen in the film maintained a 1 to 1 ratio with the latex (solids) for all four systems. This indicates that the solid films deposited onto the glass beads yield the same total drug to latex solids ratio as that in the coating dispersion.

Figure 2 depicts the in vitro release profile of acetaminophen from the four different film matrices during a 24-hour time interval. The film with a uniform drug distribution (SM1) exhibited the fastest release profile, while the three gradient film systems showed decreasing release rate of the active ingredient. The SM1 and SM2 systems attained

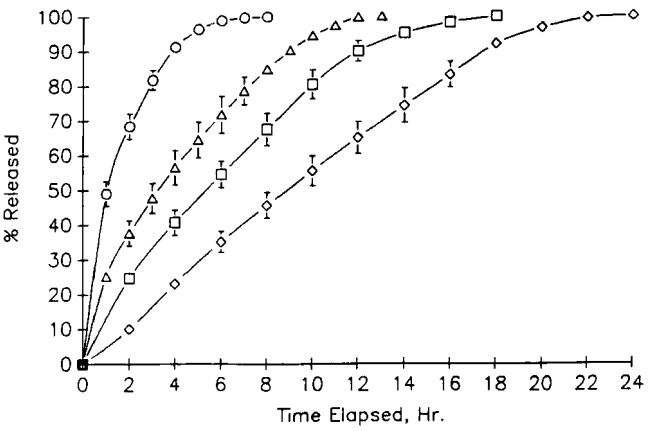

FIGURE 2

The release profile of acetaminophen from four different matrix systems. Key: ○ SM1, △ SM2, □ SM3, and ◇ SM4.

complete drug release within 12 hours, whereas SM3 yielded about 85% and SM4 achieved about 60% of the total amounts of drug released. A typical matrix diffusion controlled drug release profile was shown by SM1. For SM2 and SM3 systems, in spite of the initial fast release rate observed during the first 2 hours, the release of APAP tended to exhibit a linear relationship with the time elapsed up to 90% of the total amounts drug released. In the case of SM4, the release of APAP was shown to follow a linear relationship ($R > 0.99$) with time up to 90% of the total amounts of drug released.

For the uniform system (SM1), the distance the drug must travel to the matrix surface increases with time; thus, the drug release rate decreases with time. However, for the gradient systems the gradual

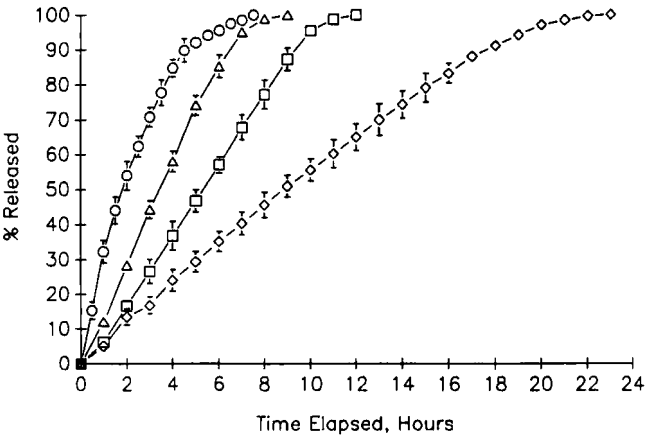

FIGURE 3

The effect of sucrose content on the release profile of acetaminophen from a concentration gradient film matrix system. Key: ◇ 0%, □ 10%, △ 15%, and ○ 20%.

increase in drug concentration from the surface to the core of the matrix compensates for the increasing diffusional distance of the drug in the matrix, due to the increase in thickness of the drug depletion zone. Therefore, drug release from these systems is shown to approach a constant rate. Furthermore, the decreasing concentration of polymer in the inner layers of the matrix also results in decreasing diffusional resistance for the drug in the inner layers of the matrix. This effect may also facilitate the linearization of the drug release profile.

Figure 3 presents the release profiles of acetaminophen from the gradient matrix systems containing different amounts of sucrose. It is apparent that a faster drug release rate was shown by the system containing a higher percentage of sucrose, and all the release profiles

were linear up to 90% of the total amount of drug released, regardless of the sucrose content in the matrix. The incorporation of a highly water soluble ingredient in a concentration gradient film matrix system was shown to result in a faster release of the active ingredient without altering the linear release characteristic. Owing to its high water solubility, sucrose readily leaches out from the film matrix and generates pores within the matrix. The overlapping of these pores give rise to water-filled channels, which provide an additional route for the diffusional transport of acetaminophen within the polymeric matrix. This additional drug release mechanism appears to be the contributory factor for the higher drug release rate exhibited by the sucrose containing matrix systems.

CONCLUSION

This paper presents a coating process for the preparation of film matrix systems with a continuous concentration gradient. A mathematical model has been developed for this coating process. The concentration gradient can be readily predicted using this model. The coating parameters listed in the model can be varied simultaneously or individually to achieve different concentration gradients of the active ingredient in the matrix. This allows further optimization of the process to produce matrix systems with constant release characteristics. The incorporation of a highly water soluble agent in a concentration-gradient matrix is another feasible means of regulating the release rate of the active ingredient from such a system.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Dr. Garnet E. Peck, Purdue University, for allowing them to use the Unit Glatt coating column.

REFERENCES

(1) C.B. Bogentoft and C.H. Appelgren, U.S. Patent 4,289,795, September 15, 1981.

(2) P.I. Lee, J. Pharm. Sci., 73, 1344 (1984).

(3) E.M.G. van Bommel and J.G. Fokkens, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 15, 316 (1988).

(4) E.M.G. van Bommel, J.G. Fokkens and D.J.A. Crommelin, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 16, 324 (1989).

(5) D.C. Scoot and R.G. Hollenbeck, Pharmaceutical Research, 6(9), S63 (1989).