DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(6), 1047-1060 (1983)

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

MICROENCAPSULATION AND IN VITRO DISSOLUTION OF OXAZEPAM FROM ETHYL CELLULOSE MICROCAPSULES

H.S. Yalabık-Kaş
University of Hacettepe, Faculty of Pharmacy,
Department of Galenical Pharmacy, Ankara-Turkey

ABSTRACT

Microcapsules of oxazepam with core:wall ratios 1:1 and 1:2 have been prepared by coacervation-phase separation method, using ethyl cellulose as a coating material. Phase separation was obtained by adding a salt solution to the dispersion of a water insoluble material in organic solution. Microencapsulation process protected oxazepam from photochemical decomposition and retarded its release. Release of the drug into simulated gastric and intestinal juice was studied. In vitro dissolution studies showed that first order release characteristics were exhibited.

INTRODUCTION

Microencapsulation is a method of wrapping small entities in individual, protective coatings (1). The function of this coating may be to protect, separate or

Copyright © 1983 by Marcel Dekker, Inc. 0363-9045/83/0906-1047$3.50/0

RIGHTSLINK

to change the physical properties or availability of the core material.

Oxazepam, which is a 1,4-Benzodiazepine-2-one derivative, is a tranquilizer. It is an important metabolite of diazepam and medazepam. Its elimination is shown to be faster than the other benzodiazepines. Oxazepam reaches to a maximum blood level in two hours and its mean plazma half-life is 3.9 hours (2). Benzodiazepines are also photochemically unstable (3-9).

In this present work, the preparation of microcapsules with ethyl cellulose at different core:wall ratios, their dissolution characteristics and the effect of particle size and the core:wall ratios on dissolution kinetics were investigated.

EXPERIMENTAL

Materials

Oxazepam (M-020), Wyeth, sieved through 180/125 μm sieve aperture; ethyl cellulose, Fluka, ethoxy number 48; methyl ethyl ketone, Merck; disodium hydrogen phosphate, Merck; potassium hydrogen phosphate, Riedel; hydrochloric acid, Merck; tripple distilled water, prepared by distillation from an all glass still.

Methods

Preparation of Oxazepam Microcapsules- Microcapsules were prepared by phase separation=coacervation method (10). Phase separation was obtained by adding 10% disodium hydrogen phosphate to the dispersion of oxazepam in methyl ethyl ketone. Into a 1 liter three necked flask, fitted with a two bladed stirrer, was placed a solution

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

of ethyl cellulose in methyl ethyl ketone. With a stirring rate of 680 rev min^{-1} and a temperature of 50°C, the core material, oxazepam, was added. Then the salt solution was added from a separating funnel, over a period of 60 minutes. After being held constant for another 60 minutes, the system was allowed to cool to room temperature with continuous stirring at the same speed in an ice bath. The hardened ethyl cellulose coated microcapsules were decanted and washed with water three times to get rid of the salts. These microcapsules then filtered and air dried.

Microcapsules with core:wall ratios of 1:1 and 1:2 were prepared. The different sizes of microcapsules present in each batch were separated by sieving on a mechanical shaker using a range of standard sieves (710-125μm) and shaking for ten minutes. The microcapsules shown in Table 1 were used in the in vitro dissolution tests.

Dissolution Procedure- A round bottomed, 3-necked flask with a 2-bladed stirrer was used. An amount of microcapsule containing 10 mg oxazepam was placed in a hard gelatine capsule and was fixed to a glass rod with a stainless steel cord. A stirring speed of 100 rev min^{-1} was kept constant during the test period. 1 liter 37°C ± 0.1°C simulated gastric juice (0.1 N Hydrochloric Acid) or simulated intestinal juice (M/15 Phosphate Buffer) were used as dissolution mediums. 5 ml samples were removed at timed intervals and 5 ml dissolution medium returned to the system immediatly. The removed samples were filtered through 45 μm Swinnex Millipore filter.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

TABLE 1

Microcapsules Used In In Vitro Dissolution Tests

Core: Wall Ratio	Sieve Aperture (μm) (Passed/Retained)	Code
1:1	355/250	M_1
	500/355	M_2
1:2	500/355	M_3
	710/500	M_4

Assay of Oxazepam- Oxazepam was assayed by measurements of the absorption at 229 nm. A lineer standard curve for absorption against concentration was obtained and the regression equation y=0.00347+0.0982x and y=0.002764 +0.0553x for 0.1 N hydrochloric acid and M/15 phosphate buffer respectively were used to determine the concentration of oxazepam in the samples.

RESULTS AND DISCUSSION

The release of active material from microcapsules is through enzymatic digestion, diffusion and dissolution of wall material (11). Enzymatic digestion is a biochemical process; dissolution of wall material is a physicochemical process. Whereas, diffusion is purely a physical process which takes place when the capsule content is sufficently soluble in body fluids and the wall material is permeable but insoluble.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

Since a comparison could be made between the different microcapsule size fractions by studing their in vitro dissolution rates, the dissolution characteristics of the microcapsules listed in Table 1 were carried on both in simulated gastric and intestinal juice. During the period of the dissolution experiments, the microcapsules of ethyl cellulose neither disintegrated nor changed their shape and size. This was an evidence that a diffusion controlled process was responsible for the release of oxazepam. This was in accordance with the work of Jenkins and Florence (12), Jalsenjak et al (13) and Alpar and Walters (14).

Microcapsules behaved like plastic matrices (15). Dissolution started as the dissolution medium penetrated through the pores of the microcapsules. Dissolution medium dissolved oxazepam as it penetrated the microcapsule wall. This produced a saturated oxazepam solution inside the microcapsule wall. This formed a concentration gradient between the interior of the microcapsule and the dissolution medium. As the dissolution proceeded, the dissolved oxazepam diffused out.

The dissolution and the in vitro release of the drug are not always easy to correlate. Therfore different equations and kinetic models should be applied(15-18). No one model is able to adequetly describe the release situation. Because of this, the dissolution data obtained have been examined and evaluated pharmacokinetically by the methods of Wagner(16), Shwarts et al(15), zero and first order release kinetics.

Release rate constants, correlation(r) and determination coefficients(r^2) were calculated and are shown in Tables 2 and 3.

RIGHTSLINK

TABLE 2

Dissolution Rate Parameters In 0.1 N Hydrochloric Acid

Kinetics		Microcapsules			
		M_1	M_2	M_3	M_4
First Order	$k_r x10^3$	5.50	4.90	2.20	1.90
	r	0.9675	0.9655	0.9706	0.9652
	r^2	0.9361	0.9323	0.9421	0.9317
Zero Order	$k_r^o x10^2$	11.74	10.02	5.13	7.64
	r	0.8980	0.9221	0.8896	0.8899
	r^2	0.8064	0.8603	0.7914	0.7917
Higuchi Equati.	Kx10	3.40	3.58	3.58	3.60
	r	0.9713	0.9645	0.9590	0.9491
	r^2	0.9435	0.9302	0.9197	0.9008

r=correlation coefficient
r^2=determination coefficient
k_r, k_r^o, K=dissolution rate constants

The zero order release plots gave a parabolic curve where the Higuchi plots were curvilinear and could not be interpreted. The Higuchi equation was developed to define the release from wax matrices. Although the hardened microcapsules present an extreme case of this Higichi model and the size remained unchanged, a linear relationship was not obtained during the course of the dissolution.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

TABLE 3

Dissolution Rate Parameters In M/15 Phosphate Buffer

Kinetics		Microcapsules			
		M_1	M_2	M_3	M_4
First Order	$k_r x10^3$	0.82	1.70	1.50	1.40
	r	0.9745	0.9472	0.9760	0.9709
	r^2	0.9497	0.8972	0.9626	0.9427
Zero Order	$k_r^o x10^2$	7.79	7.80	7.39	7.20
	r	0.9147	0.8918	0.9329	0.9257
	r^2	0.8367	0.7957	0.8707	0.8670
Higuchi Equati.	Kx10	3.39	3.73	3.83	4.32
	r	0.9859	0.9433	0.9889	0.9597
	r^2	0.9721	0.8899	0.9779	0.9211

The log-probability graphs or Wagner plots (Figures 1 and 2), gave straight line relationship for all the microcapsule samples studied and allowed an easy comparisonof the t_{50} release time (Table 4).

Dissolution rate results of all the microcapsule samples (Table1) were plotted according to the first order kinetics which gave the highest correlation and determination coefficients (Table 2 and Figures 3 and 4). Figures 3 and 4 show the release from microcapsules of different size fractions with different core:wall ratios. Within a constant core:wall ratio, the smaller microcap-

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

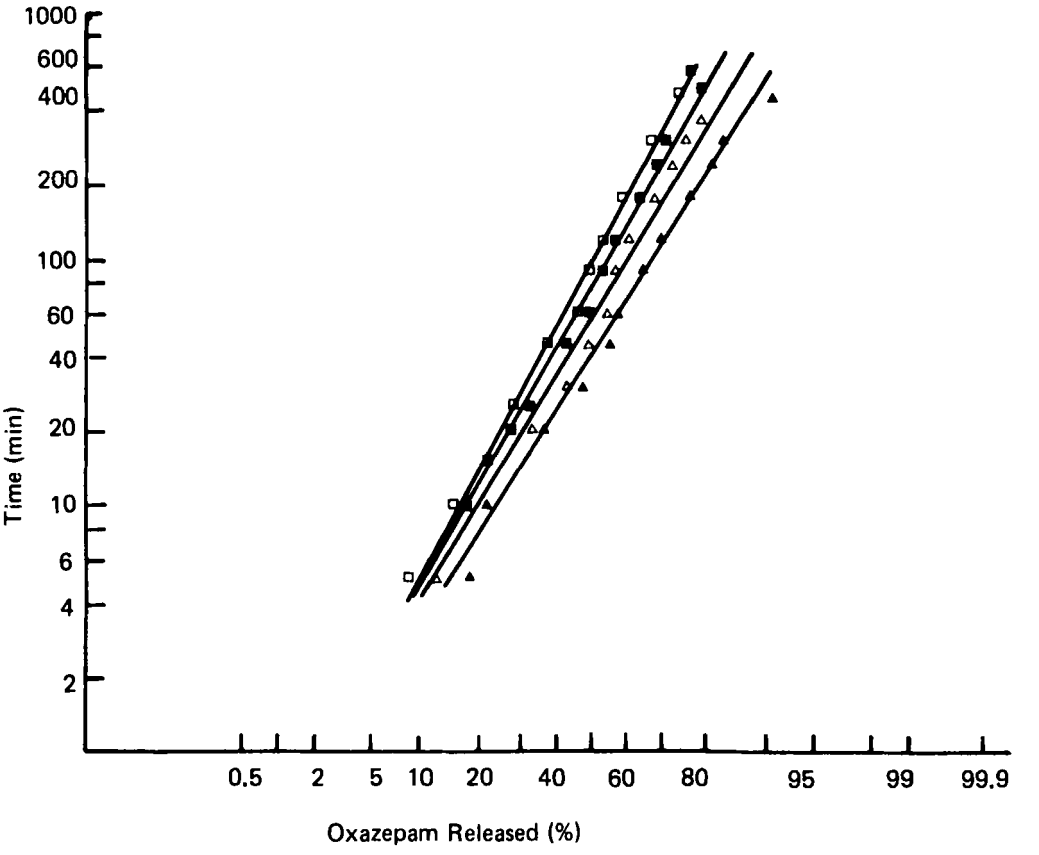

FIGURE 1

Wagner Plots of the Released Oxazepam in 0.1 N Hydrochloric Acid. Microcapsules: ▲,M_1; △,M_2; ■,M_3; □,M_4.

sules released their contents more rapidly than the larger ones. As the core:wall ratio decreased, the wall thickened and the release rate decreased. This would be seen in Figures 3 and 4 clearly; that is the microcapsules with core:wall ratio 1:2, released oxazepam slower than the ones with 1:1 ratio. The release rate decreased as the particle size increased.

Dissolution from the microcapsules is complicated because they always contain a small proportion of uncap-

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

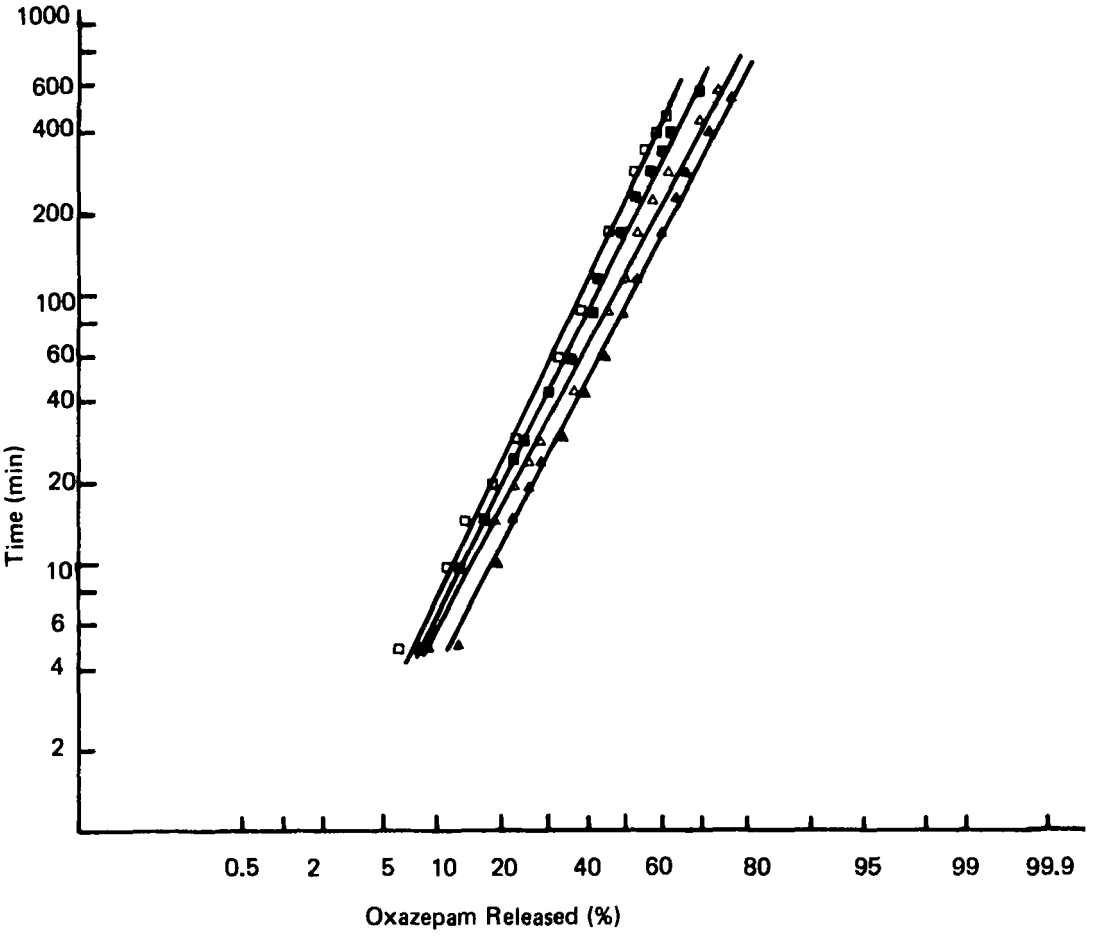

FIGURE 2

Wagner Plots of the Released Oxazepam in M/15 Phosphate Buffer. (Symbols as in Figure 1).

sulated oxazepam which could be called 'free oxazepam'(19). This could be the oxazepam that is released rapidly during the beginning of the dissolution studies. This kind of rapid followed by slow release rate could explain the two linear curves obtained by the first order kinetics.

The best fit with the highest determination coefficients was the first order kinetics plot with two straight

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

TABLE 4

Time For 50% Release Of The Microcapsules ($t_{\%50}$)

Microcapsules	$t_{\%50}$ (min)	
	0.1 N Hydrochloric Acid	M/15 Phosphate Buffer
M_1	44.00	95.00
M_2	62.00	140.00
M_3	85.00	200.00
M_4	102.00	260.00

lines having two different slopes. The first straight line gave larger slope and faster release rate than the second. The first slope might correspond to the release of 'free oxazepam' whereas the second slope might correspond to the release of oxazepam inside the microcapsule. This fast release could be usefull for the initial dose and the slow release for the maintanance dose of the prolonged release formulation.

It would appear that the modified coacervation method used in this study could be used to slow the release of the drug and that the release of the core material is a function of both core:wall ratio and microcapsule size. In addition to slowing the release of the drug, the mic-

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

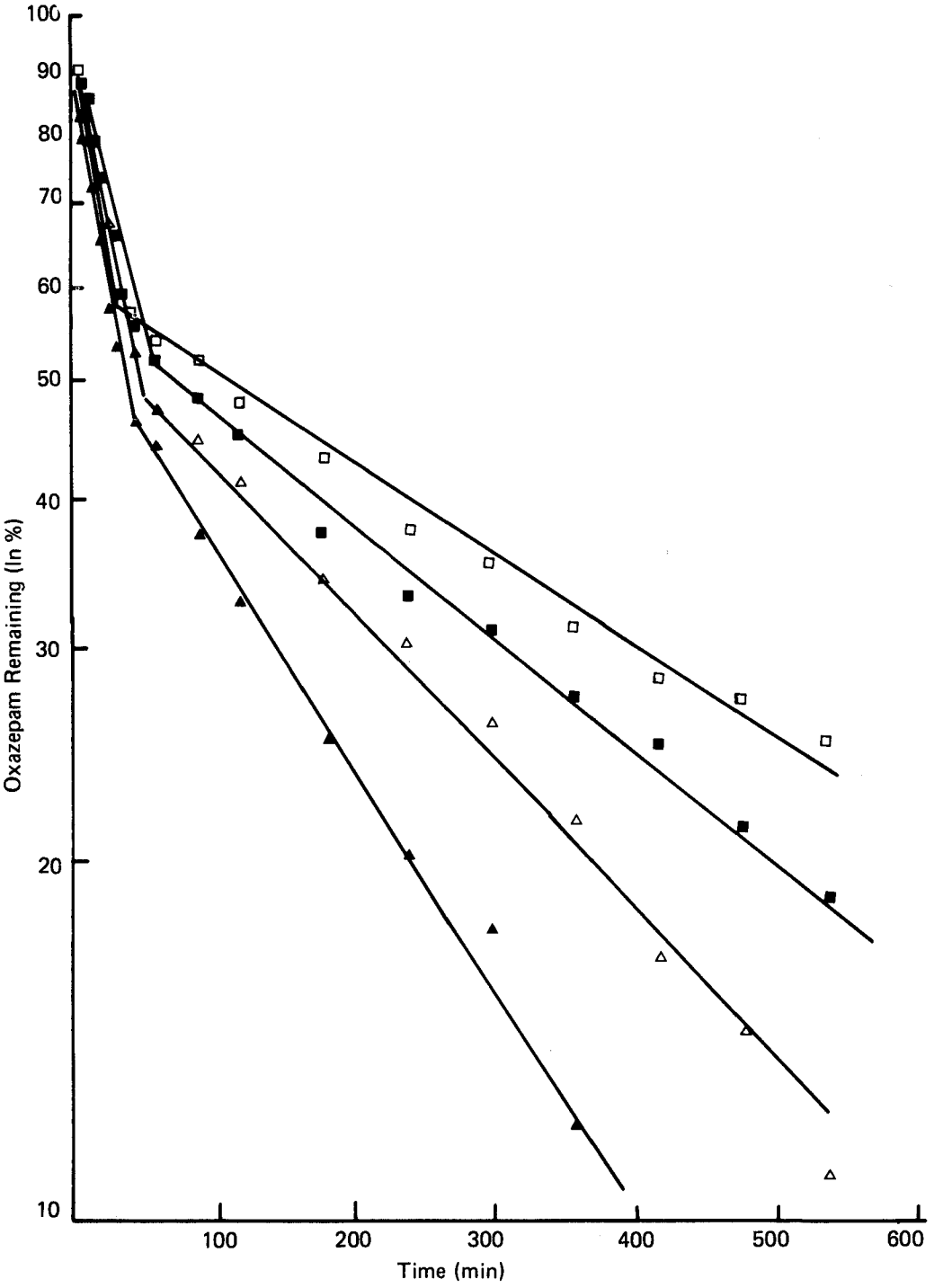

FIGURE 3

First Order Plots of the Released Oxazepam in 0.1 N Hydrochloric Acid. (Symbols as in Figure 1).

RIGHTSLINK

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

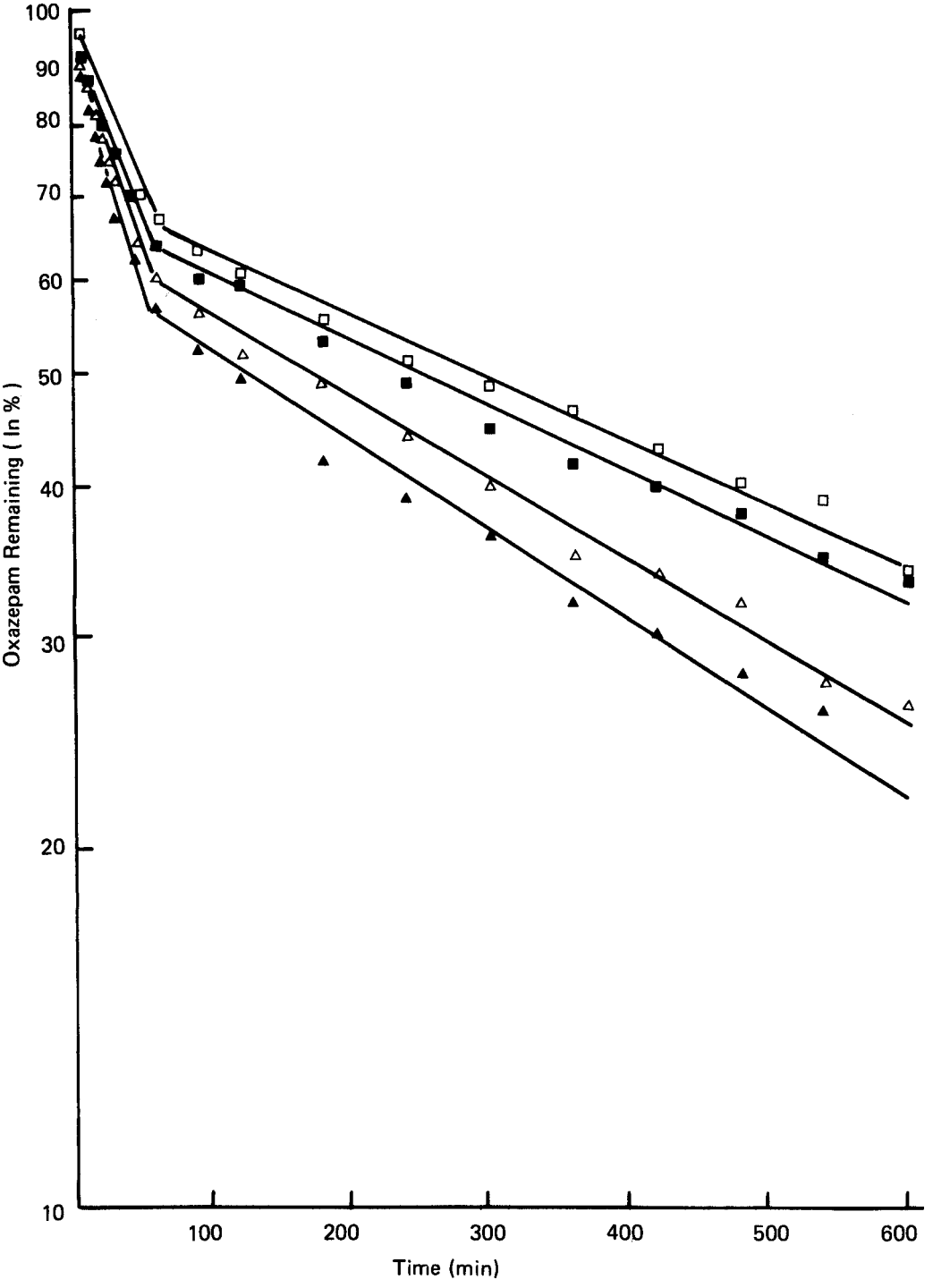

FIGURE 4

First Order Plots of the Released Oxazepam in M/15 Phosphate Buffer. (Symbols as in Figure 1).

RIGHTSLINK

roencapsulation process also protected oxazepam from photochemical decomposition (20).

REFERENCES

1. L.A. Luzzi, J. Pharm. Sci., 59, 1367 (1970).
2. J.A. Knowles and H.W. Ruelius, Arznrim-Forsch., 22, 687 (1972).
3. P.J.G. Cornelissen, G.M.J. Beijersbergen van Henegouwen and K.W. Geritsma, Int. J. Pharm., 1, 173(1978).
4. P.J.G. Cornelissen, G.M.J. Beijersbergen van Henegouwen, Proceed. 39th Int. Congr. Pharm. Sci. (FIP), 1979,p.58.
5. P.J.G. Cornelissen and G.M.J. Beijersbergen van Henegouwen, ibid., p.169.
6. G.F. Field and L.H. Sternbach, J. Org. Chem., 33, 4438 (1968).
7. L.H. Sternbach, B.A. Koechlin and E. Reeder, ibid., 27, 4671 (1962).
8. H.J. Roth and M. Adomeit, Tetrahed. Lett., 37, 3201 (1969).
9. S.C. Bell and S.J. Childress, J. Org. Chem., 27, 1691 (1962).
10. H.S. Yalabık-Kaş, in press.
11. M. Calanchi, in "Microencapsulation", J.R. Nixon, eds., Marcel Dekker Inc., New York, 1976, p. 93.
12. A.W. Jenkins and A.T. Florence, J. Pharm. Pharmacol., 25, 57P (1973).
13. I.Jalsenjak, C.F. Nicolaidou and J.R. Nixon, ibid., 28, 912 (1976).
14. H.O. Alpar and V. Walters, ibid., 33, 419 (1981).

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK

15. J.B. Schwarts, A.P. Simonelli and W.I. Higuchi, J. Pharm. Sci., 57, 274 (1968).
16. J. G. Wagner, ibid., 58, 1253 (1969).
17. F. Langenbucher, ibid., 58, 1265 (1969).
18. L.A. Luzzi, M.A. Zoglio and H.V. Maulding, ibid., 59, 338 (1970).
19. J.R. Nixon and S.E. Walker, J. Pharm. Pharmacol., 23, 147S (1971).
20. H.S. Yalabık-Kaş, Proceed. 41th Int. Congr. Pharm. Sci. (FIP), 1981, p. 98.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/20/12
For personal use only.

RIGHTSLINK