Mar. Üniv. Ecz. Der.,
13 (1), 49 - 56 (1997)

J. Pharm. Univ. Mar.,
13 (1), 49 - 56 (1997)

UZUN ETKİLİ SİPROFLOKSASİN FORMÜLASYONLARI VE İN VİTRO SALIM KİNETİKLERİ*

SUSTAINED RELEASE FORMULATIONS OF CIPROFLOXACIN AND IN VITRO RELEASE KINETICS*

Sevil AŞICI** – Özgen ÖZER** – Esra BALOĞLU**

SUMMARY

A new sustained - release dosage form of ciprofloxacin as microcapsules was prepared by means of coacervation - phase separation technique. Ethyl cellulose used as coating material. In vitro release studies for microcapsules and their formulated tablet forms were performed. Release rates were studied as a function of core:wall ratios. Dissolution paterns of the microcapsules were studied using USP XXII basket method in AGM without enzyme .Release data were examined kinetically and the ideal kinetic model was estimated for drug release. The best results for sustained action in AGM were obtained from microcapsules of 2:1 core :wall ratio.

ÖZET

Bu çalışmada yeni bir uzun etkili siprofoksasin ilaç şekli , koaservasyon - faz ayrışımı tekniği ile mikrokapsül olarak hazırlandı. Kaplama materyali olarak etil selüloz kullanıldı. Mikrokapsüllerin ve mikrokapsülle hazırlanan tablet şekillerinin salım hızı çalışmaları yapıldı. Salım hızları çekirdek:çeper oranlarının fonksiyonu olarak çalışıldı. Mikrokapsüllerin dissolüsyon modelleri enzimsiz yapay mide ortamı içerisinde USP XXII basket yöntemi ile çalışıldı. Salım verileri kinetik olarak incelendi ve ilaç salımı için en iyi kinetik model saptandı. Yapay mide ortamındaki en iyi uzun etki sonuçları çekirdek:çeper oranı 2:1 olan mikrokapsüllerden elde edildi.

* Some part of this study was presented as a poster at the Ninth International Symposium on Microencapsulation hold at University of Hacettepe in Ankara, 13-15 September 1993.

** Ege Üniversitesi, Eczacılık Fakültesi, Farmasötik Teknoloji Anabilim Dalı, 35100 Bornova – İZMİR.

INTRODUCTION

Ciprofloxacin is a fluoroquinolone with a broad spectrum of antibacterial activity (1). It has proved to be effective in a wide range of infections including those urinary, respiratory and gastrointestinal tracts and in septicemia skin , soft tissue and bone and joint infections.It has also half -life of 4 hours (2,3) . There is no recorded experience with prolonged administration of the drug in high dosage and the resultant effects of such treatment in causing toxicity or bacterial resistance (4).

Microencapsulation is now the most frequently employed method of producing sustained released form.

In this study , we planned to prepare sustained action preparation of ciprofloxacin as microcapsules and tabletted microcapsules and the influences of core : wall ratio on the release of ciprofloxacin from the microcapsules and tabletted dosage form were investigated .

The microcapsules and tablets were tested by using USP rotating basket method (5) and the dissolution results thus obtained were evaluated kinetically and the ideal method was estimated for drug release and the ideal sustained release formulation of ciprofloxacin were determined (6).

EXPERIMENTAL

Materials

Ciprofloxacin was obtained from FAKO A.Ş. , Ethyl cellulose (EC) , ethoxy number 48, type N-45 was purchased from Hercules and cyclohexane from E. Merck . All materials used were of analytical grade .

Method

Preparation of microcapsules

Microcapsules with core : wall ratio of 1:2 , 1:1 , 2:1 were prepared by the coacervation phase separation technique (7). The microcapsulation method was modified to change the temperature and the stirring rate.

Into a 500 ml three necked - flask fitted with stirrer, thermometer and a reflux, 200 ml cyclohexane was added. 4 g ethyl cellulose was added at 50 ^{0} C by continously stirring at 300 rpm. The temperature was first raised to 70^0 C slowly over 20 minutes. The temperature was raised from 70^0 C to 80^0 C over a period of 75 minutes. Ciprofloxacin, the core material , was then dispersed in the polymer solution with stirring at 300 rpm for 10 minutes. The mixture was cooled to room temperature with constant stirring to solidification of the coating . Ciprofloxacin microcapsules were separated by filtration and dried at room temperature.

The microcapsules were sieved through a combined sieve set and ciprofloxacin with particle size between 840 - 476 µ were used. Microcapsules with core : wall ratio of 1:2 , 1:1 , 2:1 (M1 , M2, M3) were prepared with the same manner.

Preparation of Tablets

Tablets (T1, T2; T3) were prepared from microcapsules with different core : wall ratios by direct compression. No lubricant , excipiant or binder was added to the microcapsules. A single-punch hand compressor was used to press the tablets.

Assay of Total Drug Content from Microcapsules

Microcapsules of different core:wall ratios containing 250 mg ciprofloxacin extracted with 10 ml of AGM without enzyme . Samples were taken as 100 µl and added 10 ml AGM without enzymes . The ciprofloxacin quantities of microcapsules were determined spectrophotometrically at 278 nm.

Dissolution procedures

Dissolution profiles of microcapsules with different core : wall ratios were determined at 37 ^{0} ± 0.1^0 C in 900 ml of AGM without enzyme using USP XXII rotating basket method at 100 rpm. The apparatus consists of cylindirical 100 ml round bottom flasks and immersed in a controlled temperature both maintained at 37 ^{0} ± 0.1^0 C. The basket was positioned to extend to exactly 2.5 cm above the flask bottom. Basket rotation was engaged and controlled at a constant 100 rpm using a dissolution stirrer drive The

samples were assayed from the dissolution medium by measuring the absorbance at 278 nm against a AGM blank without enzyme.

The dissolution data for three core:wall ratios of microcapsules and tabletted microcapsules were treated by converting observed drug concentrations at each sampling time to amounts dissolved and in turn to persentage dissolved.

The results were evaluated kinetically by zero , first- order , Hixon-Crowell, RRSBW , $Q\sqrt{t}$, $(Bt)^a$, Higuchi and Hopfenberg equations. The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer program (6).

Artificial gastric medium was prepared by dissolving 2 g of NaCl in 7 ml of concentrated HCl and sufficient water to make 1000 ml ; the pH of this solution was 1.2 .

RESULT AND DISCUSSION

Plasma elimination half- life of ciprofloxacin is 3.5 - 4.5 hours and it is easily dissolved in AGM without enzyme. Preparing microcapsules with water-insoluble coating such as EC is one way of prolonging its effect.

The recovery of ciprofloxacin from microcapsules with different core:wall ratios is shown in Table 1.

Table 1. Recovery of ciprofloxacin from microcapsules

Core: wall ratio	*Percentage recovery*
2:1	62
1:1	32
1:2	81

Dissolution results showed that encapsulation of ciprofloxacin resulted in a marked decrease in dissolution rate. The best results for sustained action in AGM were obtained from microcapsules with core:wall ratio of 2:1. Release of ciprofloxacin from microcapsules and tabletted microcapsules prepared with different core : wall ratios were shown in Fig.1 and Fig. 2 , respectively.

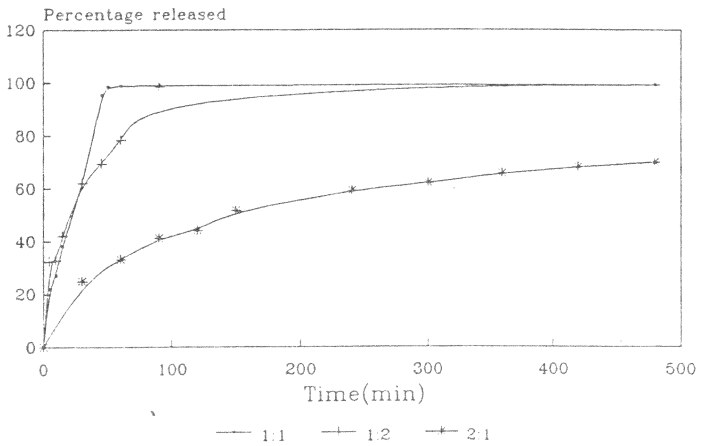

Fig .1 : Release of ciprofloxacin from microcapsules with different core:wall ratios

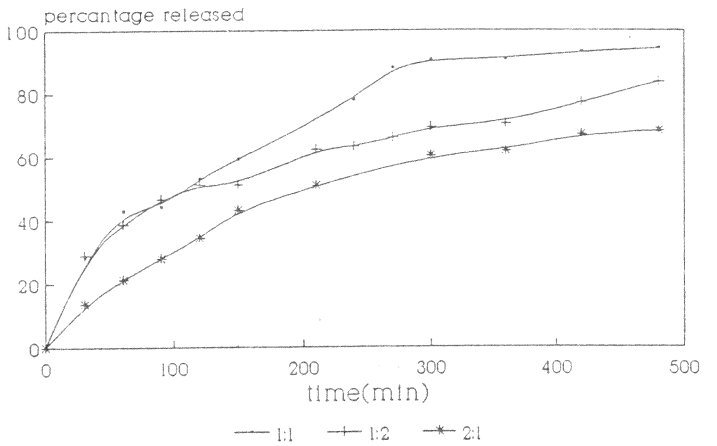

Fig .2 : Release of ciprofloxacin from tabletted microcapsules with different core:wall ratios

The release rate constants (k) , correlation coefficient (r) and determination coefficients (r^2) were calculated by means of a computer program (6). As for the kinetic evaluations the highest determination coefficient and best linear relation were observed from microcapsules and tabletted microcapsules with 2:1 core:wall ratio by RRSBW distrubution (8). Dissolution results of those were shown in Table 2.

Table2: Dissolution kinetics of ciprofloxacin tabletted microcapsules with core :wall ratio (2:1)

Dissolution kinetics	*Results*
$(Bt)^a$	A = 0.704 B = 4.578×10^{-4} r = 0.996 r^2 = 0.992
First Order	kr_1 = 0.137 hr^{-1} r = 0.987 r^2 = 0.974
Zero Order	kr_o = 17.961 hr^{-1} r = 0.963 r^2 = 0.928
Hixon-Crowell	r = 0.981 r^2 = 0.962
RRSBW	β = 0.766 r = 0.997 r^2 = 0.994
Q $\sqrt{t}$	k = 2.950 r = 0.991 r^2 = 0.982
Higuchi	r = 0.994 r^2 = 0.987
Hopfenberg spherical	k = 6.084×10^{-4} r = 0.981 r^2 = 0.962
Hopfenberg cylinderical	k = 8.192×10^{-4} r = 0.977 r^2 = 0.954
Hopfenberg slab	k = 1.197×10^{-3} r = 0.963 r^2 = 0.928

Graphically RRSBW distrubution gave a straight line with a slope of $\beta = 0.766$ and the time t = 367 min when the active ingredient was dissolved 63.2 %.

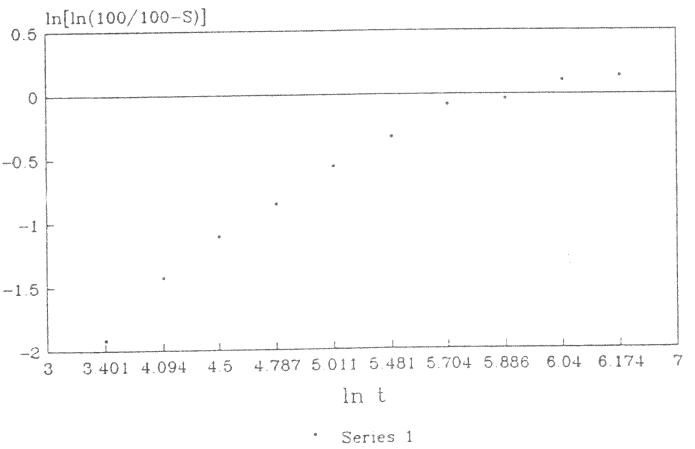

Fig .3 : RRSBW distribution of tabletted microcapsules with 2:1 core:wall ratio

Determination coefficient (r^2) , slope (β) and the time at which 63.2 percent of the active ingredient dissolved (τ) are calculated and are shown in Table 3.

Table 3 : Dissolution rate parameters of RRSBW distrubution

	r^2	β	τ
M1	0.819	0.846	25 min.
M2	0.890	1.303	20 min.
M3	0.985	0.510	326 min
T1	0.980	0.570	212 min
T2	0.953	0.846	131 min
T3	0.993	0.766	367 min

Dissolution from microcapsules and tabletted microcapsules are mainly governed by the core:wall ratio and the release appears to proceed by diffusion which is a purely physical process. It could also be expected that the microcapsules and tabletted microcapsules should behave like plastic matrices (9,10). It was shown that when compared to microcapsules in tabletted microcapsules , ciprofloxacin release is prolonged by compression.

As a result t_{50} persent values of microcapsules and tabletted microcapsules are longer then uncapsulated ciprofloxacin . This shows that the microcapsules and prepared tablets could sustain the release of ciprofloxacin.

REFERENCES

1. Fass , R. J .: Treatment of skin and soft tissue infections with oral ciprofloxacin , *J. Antimicrobial Chemotherapy , 18 Suppl. D* , 153 -157 (1986)

2. Wise, R.; Andrews, J. M.; Edwards, L.J.: In vitro activity of Bay O 9867 , a new quinolone derivative, compared with those of other antimicrobial agents , *Antimicrobial Agents Chemotherapy, 23 ,* 559 - 564,(1983)

3. Paisance, K.I. , Drusano, G.L. , Forrest, A., Bustamante, C.I. , Standiford, H. C : Effect of Dose Size on Bioavailability of Ciprofloxacin , *Antimicrobial Agents Chemotherapy, 31* , 956 - 958, (1987)

4. Daikos, G., Kathplia , S.B., Lolans, V.T., Jackson, G.G., Fosslien, E. : Long - Term Oral Ciprofloxacin : Experience in the Treatment of Incurable Infective Endocarditis , *The American Journal of Medicine, 84,* 786-790 (1988)

5. *The United States Pharmacopeia XXII (USP XXII)* ,Mac Publishing Company , Easton , Pa., 1788-9 (1990)

6. Ağabeyoğlu,T.I.: Dissol une programme Dans Le Language Basic de Microcomputer Pour la Determination des Donnes de Dissolution , Presented at *National Pharmaceutical Congress,* Istanbul (1984).

7. Jalsenjac,J., Nicolaidou,C.F.; Nixon,J.R.: The invitro dissolution of phenobarbitone sodium from ethylcellulose microcapsules, *J.Pharm . Pharmacol., 28 ,* 912 - 914 , (1976)

8. Langerbuhcher ,F. : Parametric representation of dissolution - rate curves by the RRSBW distrubution , *Pharmazeutische Industrie , 38 ,* 472 -477 (1976)

9 . Highuchi ,T .: Mechanism of sustained action medication , *J. of Pharm. Sciences , 52* , 1145 -1149 (1963)

10. Öner, L. , Yalabık - Kaş ,H.S. , Hıncal, A.A.: Formulation and release of dihydralazine sulphate from tabletted microcapsules , *J Microencapsulation , 1,* 123 - 130 (1984)

Acnowledgements

The authors would like to thank Fako İlaç Fabrikası A.Ş.,Türkiye for kindly supplying ciprofloxacin and Research Foundation of University of Ege for financial support given to this project.

(Received April 28 , 1994)