DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(4), 551-560 (1991)

CONTROLLED THEOPHYLLINE RELEASE FROM MICROCAPSULES OF ACRYLIC & METHACRYLIC ACID ESTER COPOLYMER

Sarat C. Chattaraj,[§] Sudip K. Das,[#] M. Karthikeyan,[#] Saroj K. Ghosal[§] and Bijan K. Gupta[§]

[§] *Division of Pharmaceutics, Department of Pharmaceutical Technology Jadavpur University, Calcutta - 700032, INDIA.*

[#] *Dey's Medical Stores (Manufacturing) Limited 62, Bondel Road, Calcutta - 700019, INDIA.*

ABSTRACT

The goal of this work was to develop a suitable method for microencapsulation of theophylline using copolymer of acrylate and methacrylate ester (EUDRAGIT) as the coating material. The effect of protective colloids on the process of microencapsulation was evaluated. The in vitro studies revealed significant control of drug release for the developed dosage form. Individually, the polymer coated drug particles of different core : coat ratio and different proportions of protective colloids were found to influence the pharmacokinetic parameters as revealed from the in vivo bioavailability studies in gastric-emptying controlled rabbits. In vivo bioavailability data were compared using Westlake's confidence limit.

INTRODUCTION

Theophylline is an effective brochodilator with moderate aqueous solubility. It presents a potential bioequivalence problem due to the nonreproducible rate of dissolution of the drug in the gastrointestinal fluid[1]*. The prolonged release theophylline formu-*

lations offer the advantage of less frequent dosing as well as minimum fluctuations of the serum theophylline during the dosing interval[2,3]. The object of the present investigation was to control the rate of release of theophylline from the multiple unit drug delivery systems, in a very reproducible manner in order to represent a better bioequivalence aspect.

The preparations of multiple unit products of theophylline have been reported by John et al[4], Kawashima et al[5] and Benita and Donbrow[6]. In view of the versatile properties of the copolymers of methacrylate acid esters (EUDRAGIT), the microcapsules of EUDRAGIT were expected to present a new light on the release kinetics of the drug.

The microencapsulation was achieved by nonaqueous phase separation coacervation using polyisobutylene as the coacervation inducing agent.

EXPERIMENTAL

Materials

EUDRAGIT RS 100 was received by courtesy of Röhm Pharma GmbH, Darmstadt, West Germany. Theophylline - Indian Pharmacopoeia, Polyisobutylene (mol. wt. 380,000, density 0.918 gm/ml, Aldrich, USA), Chloroform (analytical reagent, E. Merck, India), n-Hexane (analytical reagent, E. Merck, India) were produced commercially and were used without further purification.

Preparation of Theophylline Microcapsules

While stirring at 300 r.p.m., 3-8% w/w polyisobutylene was added into a homogeneous 5% w/w solution of EUDRAGIT RS 100 in choloroform. Powdered theophylline of 120 mesh size dispersed into the solution. The phase separation and subsequent deposition of the liquid polymer onto the surface of the core material and rigidization of the deposited polymer was achieved by dropwise addition

of chilled n-hexane, while stirring at 600-650 r.p.m. After the formation of embryonic microcapsules, they were seperated from the solution by decantation and washed with three 250 ml portions of chilled n-hexane to remove any polyisobutylene adsorbed at the interface and also any placebo coacervate. The microcapsules were air dried at ambient temperature for 30 minutes and finally dried at 50°C in vacuum drier for one hour.

In vitro Dissolution Study

In vitro drug release profile was evaluated using USP XX rotating basket dissolution apparatus[7] with the basket covered with 100 mesh nylon cloth to prevent escaping of the microcapsules. The basket was rotated at 100 ± 2 rev. $min.^{-1}$. Five hundred ml of the dissolution fluid was taken and the process of increasing the pH conditions was followed[8]. A constant temperature of 37 ± 1°C was maintained. Five ml of the dissolution aliquots were removed at 30 min interval and the amount of theophylline released was assayed spectrophotometrically at 271 nm.

Assessment of Bioavailability in Rabbits

Male albino rabbits were used with a fortnight washout period between each use and the state of coprophagy maintained properly[9]. The administration of microcapsules of theophylline was based on a crossover design to minimize the influence of any residual or cumulative effects of preceding doses.

A single dose, equivalent to 40 mg of theophylline per kg bodyweight, was put into hard gelatin capsule. The mouth of the animal was pushed open with a wooden gag and capsule was placed on the tongue. Sufficient water was administered to flush the capsule. During the blood sampling only water was allowed ad libitum.

Blood samples were drawn from the marginal ear vein at predetermined time and were frozen immediately till the analysis were

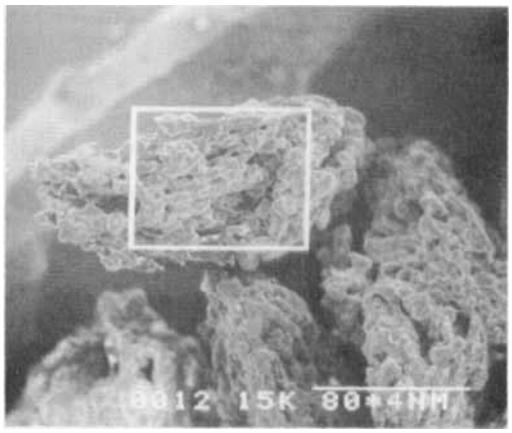

Fig. 1 - ***Scanning electron micrograph of EUDRAGIT microcapsules showing surface topography.***

performed. After precipitation and seperation of the plasma proteins by centrifugation, the content of the drug in blood was determined spectrophotometrically[10].

RESULTS AND DISCUSSIONS

The scanning electron micrograph in Fig. 1 revealed complete encapsulation of the theophylline particles. The microcapsules were irregularly shaped with aggregation of the smaller ones.

Microencapsulation using methacrylate ester copolymer coacervation in the presence of a protective colloid like polyisobutylene prevents the formation of empty stabilized coacervation droplets from interaction with the microcapsules and favours the formation of a continuous uniform coating over the surface of the core material. The use of polyisobutylene (5.5% w/w) increased the percentage of small microcapsules, though the recovered ones were detected to be polynuclear. Lower percentage of polyisobutylene failed to produce uniform microcapsules, rather aggregates. Similarly, with higher percentage of polyisobutylene the higher viscosity produced in the system lowered the yield of the product.

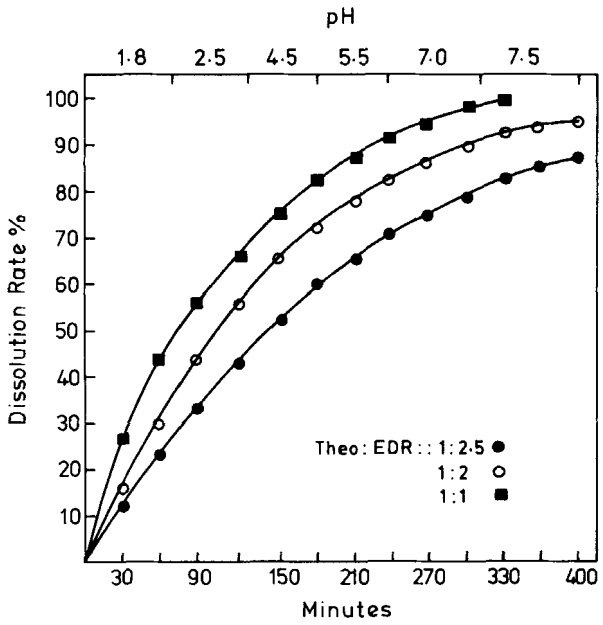

Fig. 2 - ***Effect of core : coat ratio on in vitro theophylline release; polyisobutylene 5.5% w/w, sieve size 32/44.***

The drug content of the microcapsules was maximum at 5.5% w/w of polyisobutylene at certain fixed core : coat ratio.

Comparative study of the dissolution profiles of the drug from different batches of the microcapsules prepared with various core : coat ratio and percentages of polyisobutylene are presented in Fig. 2 & 3, respectively. Beyond the optimum range of polyisobutylene, the drug release upto 400 mins were noted for all the microcapsules. The first order kinetics and Higuchi diffusion model was followed 77.5% and 86.4%, respectively, when the experimental data were subjected to statistical validity tests for different model fitting by program RELAN[11]. The first order diffusion controlled dissolution was suggested to occur.

The pharmacokinetic data in table 1 depicted a significant difference of maximum plasma level (C_{max}) and the time to reach

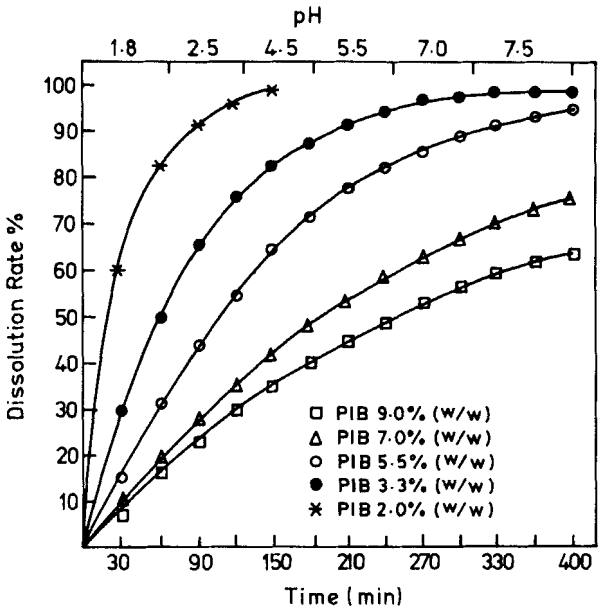

Fig. 3 - ***Effect of polyisobutylene concentration on in vitro theophylline release; core : coat ratio 1 : 2.5, sieve size 32/44.***

the C_{max} (t_{max}), among different batches of microcapsules. It was also observed that the plasma level of theophylline slowly declined during a very long period with the microcapsules having a core : coat ratio of 1:2.5. The comparative AUC values indicate that the better maintenance of plasma level of the drug was achieved from microcapsulated drug.

Both classical hypothesis testing of variance, at 0.1 level, and Westlake's confidence intervals on the data obtained from 12 rabbits for the formulations having the core : coat ratio 1:1, 1:2 and 1:2.5 indicate that the formulation having core:coat ratio 1:2.5 significantly better than the other formulations tested, considering the following Westlake's confidence parameters :

Westlake's 95% Confidence Limit[12]

$\bar{X}_s = 7.527$; $\bar{X}_n = 14.08$; $S = 3.69$

TABLE - 1 : ***PHARMACOKINETIC PARAMETERS OF THEOPHYLLINE AFTER ORAL ADMINISTRATION IN RABBITS***

Core : Coat ratio	Number of rabbits	C_{max} ug/ml	t_{max} hr	AUC 0-∞ ug.hr.ml.	K_{el} hr^{-1}	$t_{1/2}$ hr
1 : 1	12	26.5±0.8	4.22±0.32	172.05±12.28	0.095±0.01	7.52±1.58
1 : 2	12	21.03±0.5	6.9±0.42	209.8±7.09	0.064±0.03	10.62±0.46
1 : 2.5	12	18.0±0.31	8.03±0.28	230.74±8.69	0.049±0.03	14.08±1.61
Pure Drug	12	42.8±1.92	1.86±0.44	204.2±9.6	0.101±0.04	6.86±0.27

Each data represents average of 12 observations ± S.E.M.

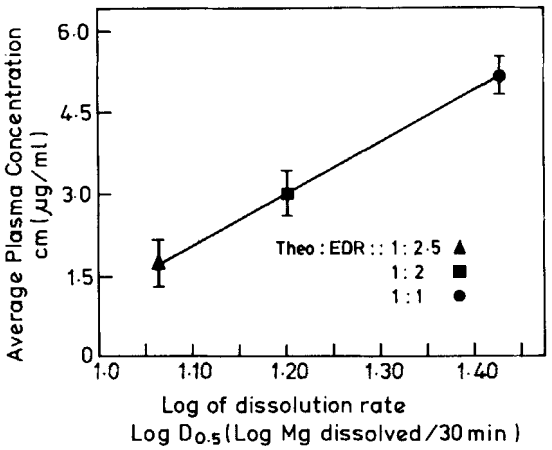

Fig. 4 - ***Correlation of dissolution rate and mean plasma theophylline levels in stomach emptying controlled rabbits.***

By Equating

$$2(\bar{X}_s - \bar{X}_n) = (k_1 + k_2)\, S/\sqrt{6}$$

then $k_1 + k_2 = 8.69$

$\Delta = 0.0145$

where,

$\bar{X}_s$ = *Mean for product having least desired properties (core:coat :: 1:1)*

$\bar{X}_n$ = *Mean for product having better desired properties (core:coat :: 1:2.5)*

S = *Standard Deviation for the set*

k_1 & k_2 = *Probability of integating 't' value (k_1 & k_2 is so chosen that the integral of 't' distribution from k_2 to k_1 is 0.95)*

Δ = *Difference of Limits*

With k_1 and k_2 values, from the 't' tables, we could draw the inference that the experimental data for core:coat ratio 1:2.5 show significantly better controlled release properties than for core:coat ratio 1:1 and is within Westlake's 95% confidence limits.

The results of the pharmacokinetic analysis also suggests that the microcapsules prepared with the core:coat ratio of 1:2.5, and with 5.5% w/w of polyisobutylene illustrates significant controlled release characteristics.

Correlation of the in vivo plasma level of the drug and the in vitro dissolution rate is depicted in Fig. 4. Significant correlation coefficient, 0.998 ($p < 0.10$), indicates the validity of in vitro routine assay of the drug and availability of theophylline from such dosage forms in vivo.

In conclusion, the microcapsules of methacrylate esters containing theophylline satisfactorily maintain the plasma level of the drug for a prolonged period. The controlled release characteristics of the drug was significantly reproducible.

ACKNOWLEDGEMENT

We wish to thank Röhm Pharma GmbH for their generous supply of EUDRAGIT. Financial assistance from the University Grants Commission is gratefully acknowledged.

REFERENCES

1. *R. Baptista and D. F. Driscoll, Am, Pharm.* **24**, *285 (1984)*
2. *M. Weinberger, Pharmacotherapy,* **4**, *181 (1984)*
3. *J. M. Cummisky and V. Popa, J. Asthma,* **21**, *243 (1984)*
4. *P. M. John, M, Minatoya, F. J. Rosenberg, J. Pharm. Sci.* **68**, *475 (1979)*
5. *Y. Kawashima, T. Handa, A. Kasai, H. Takenaka, S. Y. Lin, Y. Ando, J. Pharm. Sci.* **74**, *264 (1985)*
6. *S. Benita and M. Donbrow, J. Pharm. Sci.,* **71**, *205 (1982)*
7. *United States Pharmacopeia - 20th rev., USP Convention Inc., Rockville, MD, p. 959*

8. S. K. Das and B. K. Gupta, Drug Dev. Ind. Pharm., **14**, 537 (1988)

9. T. Maeda, H. Takenaka, Y. Yamahira, T. Noguchi, J. Pharm. Sci., **66**, 69 (1977)

10. C. S. Frings, R. C. Keefer and J. M. Saloon, Clin, Toxicol. **8**: 553,(1975)

11. S. K. Das, S. Palchowdhury, S. C. Chattaraj, B. K. Gupta (Communicated)

12. W. J. Westlake, J. Pharm. Sci., **61**, 1340 (1972)