Arch. Pharm. Res. Vol. 16, No. 1, pp. 50-56, 1993

Studies on the Development for Sustained Release Preparation (II): Preparation and Evaluation of Eudragit Microcapsules of Sodium Naproxen

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(Received November 4, 1992)

The microencapsulation of sodium naproxen with Eudragit RS was studied by coacervation/phase separation process using Span 80 in mineral oil/acetone system. Various factors which affect the microencapsulation, e.g., stirring speed, and surfactant concentration, Eudragit RS concentration and loading drug amounts were examined. For the evaluation of the prepared microcapsules, release rate, particle size distribution and surface appearance as well as *in vivo* test were carried out. The addition of n-hexane and freezing of microcapsules accelerated the hardening of microcapsules. The optimum concentration of Span 80 to prepare the smallest microcapsules was the same value with the CMC of Span 80 in solvent system. When 1.5% (w/w) Span 80 was used, the smallest microcapsules were formed (30.02± 5.05 μm in diameter) belonging to the powder category showing smooth, round and uniform surface. The release of sodium naproxen was retarded by microencapsulation with Eudragit RS. The Eudragit RS microcapsules showed significantly increased AUC and MRT and decreased Cl/F in rabbits.

Key words: Microencapsulation, Sodium naproxen, Eudragit RS, Sustained release, Coacervation

INTRODUCTION

One of the technological means for the preparation of sustained action dosage form, microencapsulation of drug with polymeric wall material is widely used (Vandegaer, 1973).

Naproxen, a nonsteroidal anti-inflammatory agent, is commercially available as a acid or sodium salt. When the sodium salt is administered, it is absorbed more rapidly in the GI tract than the acid form. When single oral dose of 100 or 300 mg is administered to man, naproxen is extensively bound to plasma protein but fully absorbed and the response of dose-plasma level is linear (Runkel *et al.*, 1972; Abakke *et al.*, 1983; Dahl *et al.*, 1990).

Eudragit RS, acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, is insoluble in the digestive tract (Chafi *et al.*, 1988) and excreted with feces, but they swell in aqueous medium and exhibit a distinct permeability (Okor and Obi, 1990) for water and water soluble substances. Their swelling and permeability properties are independent on the pH conditions in the gastrointestinal tract. (Goto *et al.*, 1986a, 1986b).

In the present study, in order to prepare the sustained release form of sodium naproxen, microencapsulation of drug with Eudragit RS and evaluation were carried out *in vitro* and *in vivo*. The particle size of microcapsules reproted by other studies upto now was quite large (Dakkuri *et al.*, 1978; Nixon and Agyilirah, 1984; Carli *et al.*, 1988). Therefore, we tried to find a useful, simple and rapid preparation method of microcapsules having small size. Various factors which affect the microencapsulation such as stirring speed, surfactant concentration, critical micelle concentration (CMC) of surfactants, Eudragit RS concentration and drug loading amounts were examined. In order to evaluate the sustained action of drug and improved bioavailability, Eudragit microcapsules were administered orally to rabbits and compared with those of sodium naproxen powder. Bioavailability of naproxen was evaluated by the area under the curve (AUC), mean residence time (MRT), and clearance/bioavailability (Cl/F) calculated from the plasma concentrations of naproxen.

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MATERIALS AND METHODS

Materials

Sodium naproxen and sodiun heparin were of pharmaceutical grade provided by Chongkundang Pharm. Ind. Co., Ltd. (Korea) and Eudragitk RS 100 was from Roehm Pharm. Co. (Germany). Sorbitan monooleate (Span 80) and light mineral oil were of reagent grade. Methanol and acetonitrile were of HPLC grade from Merck Co., Ltd. (Germany).

Apparatus

Dissolution tester (Prolabo dissolution tester), UV spectrophotometer (Perkin-Elmer, Lambda 5), microbalance (Beckman), mechanical stirrer (Dongyang Science Co.), optical microscope (Nikon), scanning electron microscope (JSM 35C) and HPLC (Pye Unicam) were used.

Preparation of Microcapsules

The dispersion media, 100 ml of light mineral oil containing Span 80, were added to a 500 ml round bottom kettle flask. The dispersion medium was stirred at 500 rpm, and 5 ml of Eudragitk RS solution in acetone were added to the round flask. After stirring for 5 min, sodium naproxen powder (500 mg) was added and subsequently stirred for 10 min. Thereafter, 30 ml of n-hexane were added to the system as a nonsolvent to precipitate the microcapsules. The addition of n-hexane at the final stage facilitated the hardening of microcapsules and aceelerated sedimentation (Bogataj *et al.*, 1989). The prepared microcapsules were stored under freezing condition in order to avoid agglomeration. The microcapsules were filtered under reduced pressure and washed with n-hexane for several times. Final products were obtained by drying under the reduced pressure.

Determination of CMC

The CMC of Span 80 in the system of mineral oil and acetone (9:1 v/v %) was determined by measuring the interfacial tension with microbalance using the ring method.

Assay of Sodium Naproxen Content

The ground microcapsules corresponding to about 100 mg of sodium naproxen were added to 250 ml volumetric flask. Thereafter, 0.5 ml of acetone was added and the powder was suspended in 200 ml of distilled water. To rupture the shells completely, the suspension was sonicated for 10 min (Merkle and Speicer, 1973). The concentration of naproxen was determined using spectrophotometer at 230 nm after proper dilution.

Dissolution Test

The release of drug from microcapsules was determined using dissolution tester in 900 ml of artificial gastric and intentinal fluids of pH 1.2 and 6.8 (Takenaka *et al.*, 1980; Maharai *et al.*, 1984) at 37℃ and 100 rpm. Aliquots of 3 ml were withdrawn and the same volume of fresh medium was added at various time intervals. The difference caused by this manipulation was corrected during data analysis.

Microscopic Studies of Microcapsules

Optical and scanning electron microscopy were used to evaluate the quality of coating prepared under various conditions (Yoshioma *et al.*, 1981). A small but representative portion of powder randomly chosen from different fields was transferred to a slide glass and the size was determined for about 200 particles by microscopic observation.

Treatment of Rabbit

Eight Newzealand male rabbits weighing about 2± 0.28 kg were used. They were devided into two groups and fasted at least 12 hrs before experiments. One group recieved intact sodium naproxen powder (7 mg/kg) and the other group recieved microcapsules corresponding to 7 mg/kg of drug. Drugs of two test samples were filled respectively, into the smallest gelatin capsules and they were hold to catether associated with piston occupied with 15 ml water. Ear artery of rabbit was enlarged by heat for canulation and then scalp vein needle was inserted into artery. Heparin solution (20 IU per ml of normal saline) was infused temporarilly. Thereafter, the mouth of rabbit was opened using channel, rolled it to pull out the tong, inserted catether through the hole, and pushed the piston immediately. After dosing, blood samples were taken from each subject at specified time intervals, and were immediately centrifuged for 2 min at 8,000 rpm and frozen below −20℃ until assay.

HPLC Determination of Naproxen

The plasma concentration of naproxen was determined by HPLC method (Ismail *et al.*, 1985) using indomethacin as an internal standard. One hundred μl of plasma was mixed for 5 sec on a vortex mixer with 10 μl of methanol containing 50 μg/ml of indomethacin. The tube was centrifuged at 8,000 rpm for 10 min. An aliquot (10 μl) of the supernatant was injected into the reversed phase column and the flow rate was maintained at 2 ml/min. The mobile phase was 6:4 ratio of methanol and 0.05 M phosphate buffer (pH 5.5). Concentrations of naproxen and indomethacin were detected at 230 nm and quantified by the internal standard method using peak height ratios.

Determination of Pharmacokinetic Parameters

The moment analysis (Riegelman and Collier, 1980) for determination of pharmacokinetic parameters was carried out using the RSTRIP computor program (Lamson, 1987).

RESULTS AND DISCUSSION

Effect of Stirring Speed on the Microencapsulation

Low stirring speeds (below 150 rpm) were not satisfactory. Proper dispersion and emulsification occured between 400 and 800 rpm and the appropriate microcapsules were produced. Smaller microcapsules (Fig. 1) were produced at the higher speed. But, above 850 rpm, a suitable microcapsule was not produced. By this preliminary experiment, 500 rpm was adopted for a optimum condition of preparing microcapsules of good appearance and appropriate size.

Effect of Surfactant on the Microencapsulation

It is desirable to use as small amount of surfactants as possible considering toxicity, cost and ease of handling. The photographs of microcapsules prepared using different surfactant concentrations are shown in Fig. 2. The mean size of microcapsules was the smallest when 1.5% (w/w) Span 80 was used (Table I). The relationships between interfacial tensions and concentrations of Span 80 are shown in Fig. 3. The interfacial tension was not changed in the range of 0 to 1.4% (w/w) of Span 80, but declined rapidly in the range of 1.4 to 1.6% (w/w) and became constant above 1.6% (w/w). The CMC and the optimum concentration of Span 80 to prepare the smallest microcapsules coincided to be about 1.5% (w/w). Therefore the determination of CMC of a surfactant in solvent system is very important to predict the optimal concentration of Span 80 to prepare the smallest microcapsules.

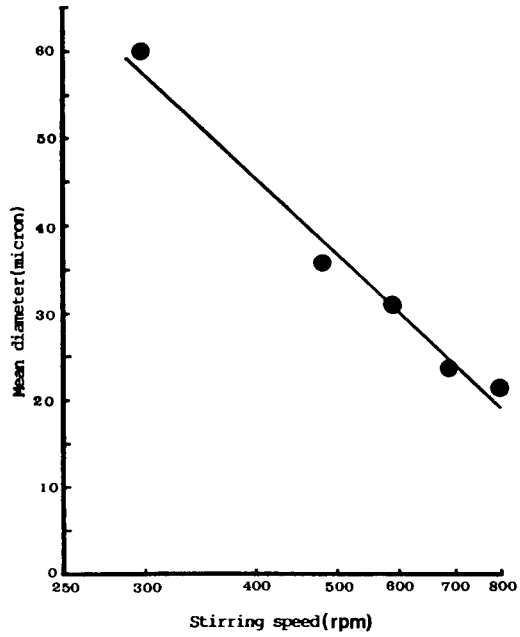

Fig. 1. Effect of stirring speed on the mean diameter of microcapsules prepared with 10% Eudragit RS and 1.5% Span 80.

Effect of Polymer Concentration on the Microencapsulation

The effect of the Eudragit RS concentration on the size of microcapsules was examined while other conditions were kept constant. The histograms of size distribution of microcapsules prepared with various concen-

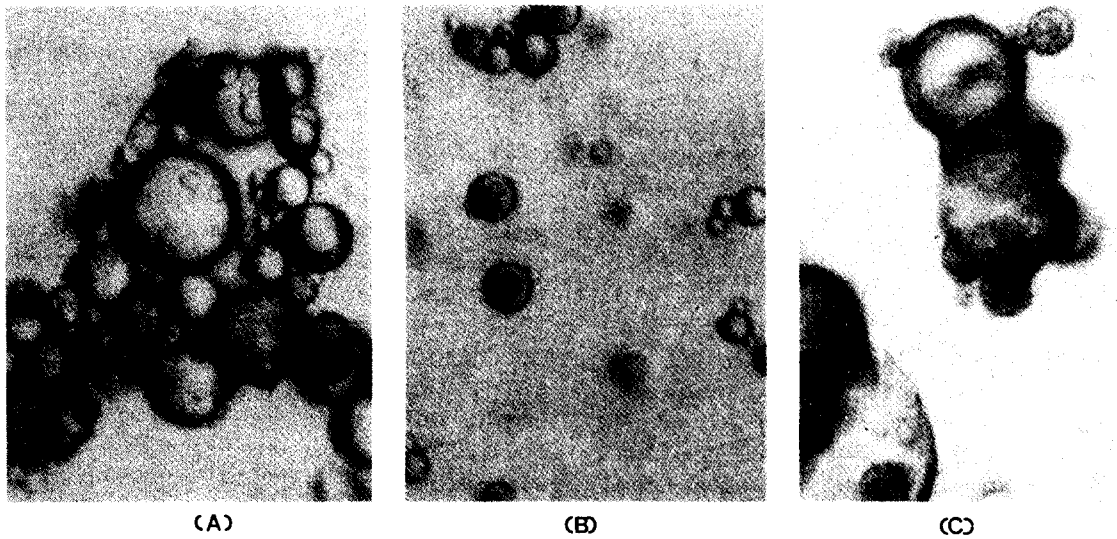

Fig. 2. Photographs of microcapsules prepared using different surfactant concentrations with 10% Eudragit RS at 500 rpm. A. 0.3% surfactant; B. 1.5% surfactant; C. 3% surfactant.

Table I. Mean size of microcapsules prepared with 10% Eudragit RS using various % of Span 80 at 500 rpm

Conentration of Span 80 (%)	Mean diameter± S.D. (μm)
0	83.52± 12.21
0.3	54.57± 8.21
0.6	50.19± 7.75
1.0	47.15± 6.66
1.5	30.02± 5.05
3.0	77.97± 14.65

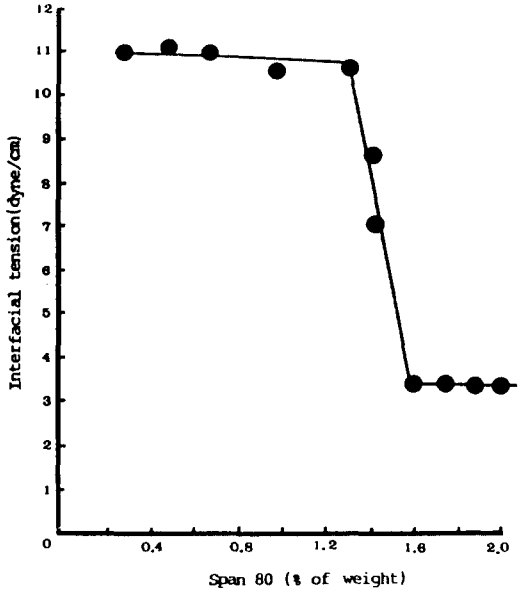

Fig. 3. Interficial tension of Span 80 in the mineral oil-acetone system.

trations of Eudragit RS are shown in Fig. 4 and mean size are shown in Table II. The fraction of larger size was increased by increasing the concentration of Eudragit RS solution (Fig. 4). The average diameter of 10% Eudragit RS microcapsules was about 36.25 μm and that of 20% Eudragit RS microcapsules was about 38.31 μm. Microencapsulation of sodium naproxen with Eudragit RS using 1.5% Span 80 was an effective method for preparing the small particle size belong to the powder category.

Number and Weight Distributions of Microcapsules

The mean geometric diameter of 10% and 15% Eudragit RS microcapsules were graphically determined from the individually logarithmic probability plots of the percent cumulative undersize curves (Fig. 5). In log-probability of 10% Eudragit RS microcapsules, d_g=27.6 μm and σ_g=1.33 for the number distribution data and d_g'=50.1 μm and σ_g'=1.318 for the weight distribution data (Fig. 5A). In that of 15% Eudragit RS microcapsules, d_g=32.3 μm and σ_g=1.34 for the number distribution data and d_g'=57.9 μm and σ_g'=1.38 for the weight distribution data (Fig. 5B).

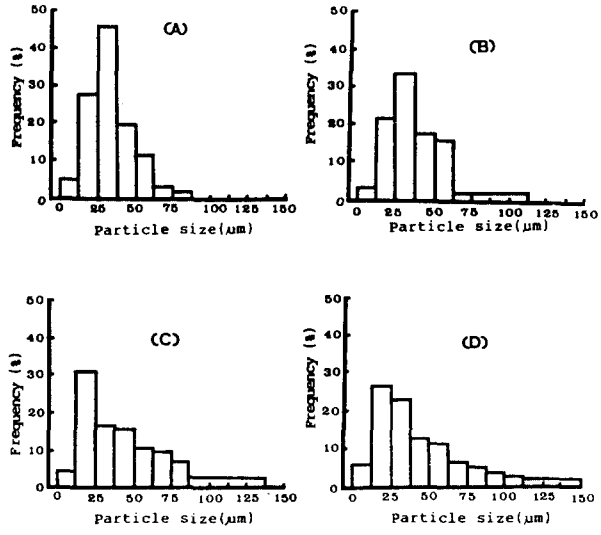

Fig. 4. Histograms for the size distribution of microcapsules prepared with Eudragit RS of various concentrations and 1.5% Span 80 at 500 rpm.
A. 10% Eudragit RS microcapsule; B. 15% Eudragit RS microcapsule; C. 20% Eudragit RS microcapsule; D. 25% Eudragit RS microcapsule.

Table II. Drug content and mean size of microcapsules prepared with various concentrations of Eudragit RS using 1.5% Span 80 at 500 rpm

Concentration of Eudragit RS (%)	Theoretical content (%)	Experimental content± S.D. (%)	Mean diameter ± S.D. (μm)
10	50	51.98± 0.42	36.25± 5.64
15	40	40.20± 0.77	37.13± 5.94
20	33.3	32.83± 1.62	38.31± 8.67
25	28.6	29.61± 2.94	46.94± 9.62

Drug Release

The dissolution pattern of sodium naproxen from different Eudragit microcapsules in artificial gastric and intestinal fluids of pH 1.2 and 6.8 at 37℃ and 100 rpm are shown in Fig. 6. The release of sodium naproxen from Eudragit RS microcapsules was retarded in dissolution medium of pH 1.2 and 6.8 as compared with intact drug powder. Intact drug powder was dissolved completely within 2 hrs but the release of drug from 10% Eudragit RS microcapsules was about 65% in 6 hrs (Fig. 6). The release of sodium naproxen was dependent on the loaded drug amount in the microcapsules (Fig. 7). In case of high drug content, drug diffusion through the wall might be easier due to the increase in the number of pores produced during release.

Surface of Microcapsules

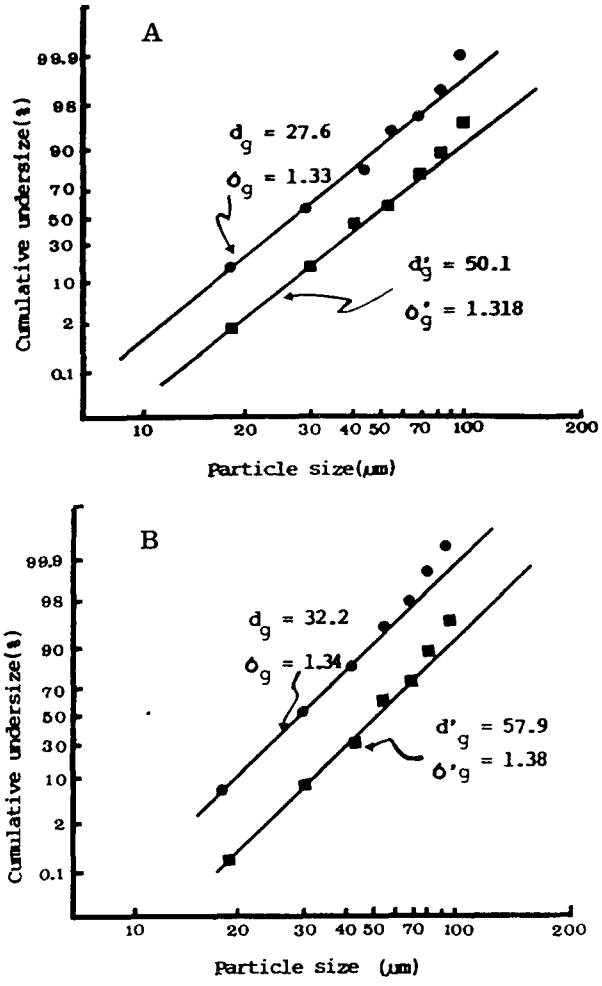

Fig. 5. Log probability plots of microcapsules prepared with various concentration of Eudragit RS.
(A) 10%; (B) 15%; ●, number distribution; ■, weight distribution.

All core particles were individually and well coated suggesting the similarity of thickness around the cores (Fig. 2). Eudragit RS microcapsules prepared using 1.5% Span 80 showed smooth, round and small particles, while irregular and rough surface in microcapsules prepared without surfactant. Microcapsules were swollen but the surface was not almost altered even after dissolution (Fig. 8).

Pharmacokinetic Parameters

The AUC, MRT and Cl/F of microcapsules after oral administration were significantly ($p<0.05$) different from those of naproxen (Table III). Peak plasma level of intact sodium naproxen powder was detected after 1 hr and that of microcapsule was detected after 4 hrs (Fig. 9). The AUC of sodium naproxen was 3,529.41 ± 350.60 and that of microcapsules was 5,222.61± 413.61 μg min/l. The MRT of two formulations, which means the time for elimination of 63.2% of total drug

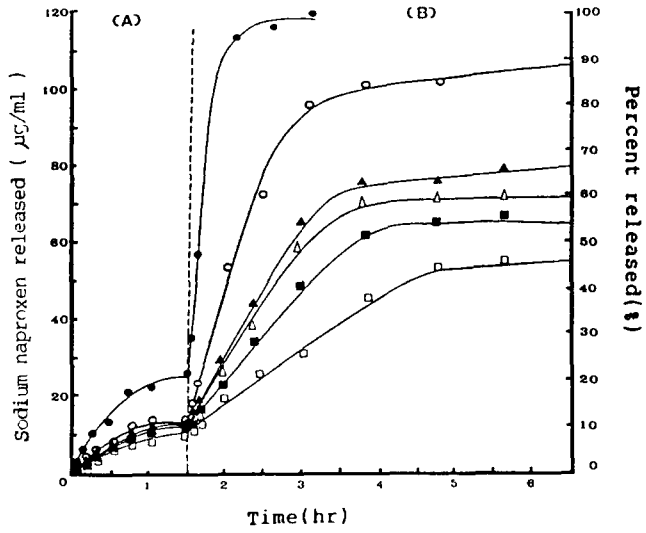

Fig. 6. Release of sodium naproxen from microcapsules prepared with various concentration of Eudragit RS and 1.5% Span 80 in dissolution medium (pH 1.2 and 6.8) at 100 rpm and 37℃.
(A) Dissolution medium (pH 1.2); (B) Dissolution medium (pH 6.8): ●, sodium naproxen; ○, 5% Eudragit RS microcapsule; ▲, 10% Eudragit RS microcapsule; △, 15% Eudragit RS microcapsule; ■, 20% Eudragit RS microcapsule and □, 25% Eudragit RS microcapsule.

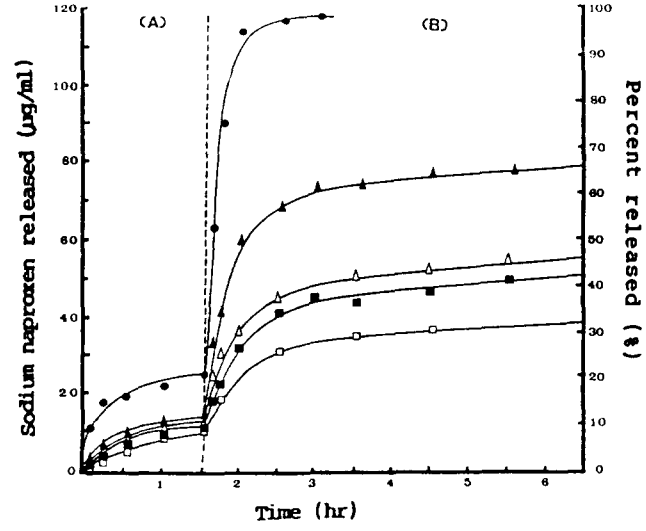

Fig. 7. Release of sodium naproxen from microcapsules prepared with 10% Eudragit RS using various drug amounts loaded in dissolution medium of pH 1.2 and 6.8 at 100 rpm and 37℃.
(A) Dissolution medium (pH 1.2); (B) Dissolution medium (pH 6.8): ●, sodium naproxen; ▲, core:wall ratio (1:1); △, core:well ratio (0.5:1); ■, core:well ratio (0.4:1) and □, core: well ratio (0.3:1).

in the body, was 511.00± 32.8 and 579.05± ± 13.94 min. The Cl/F of sodium naproxen was 2.04± 0.22 and that of microcapsule was 1.37± 0.10 ml/min. The AUC

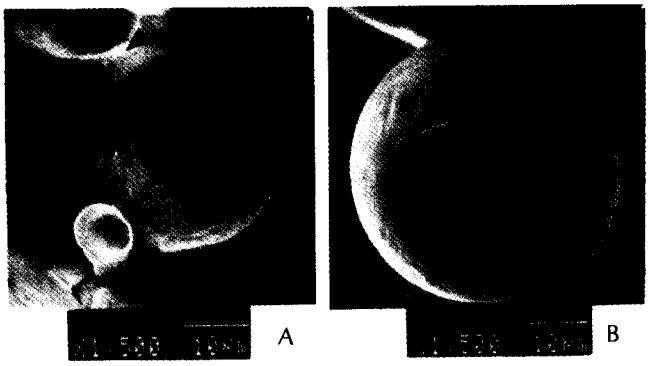

Fig. 8. Scanning electron micrographs of microcapsules prepared with 10% Eudragit RS and 1.5% Span 80 at 500 rpm (×1,500).
A. before dissolution; B. after dissolution.

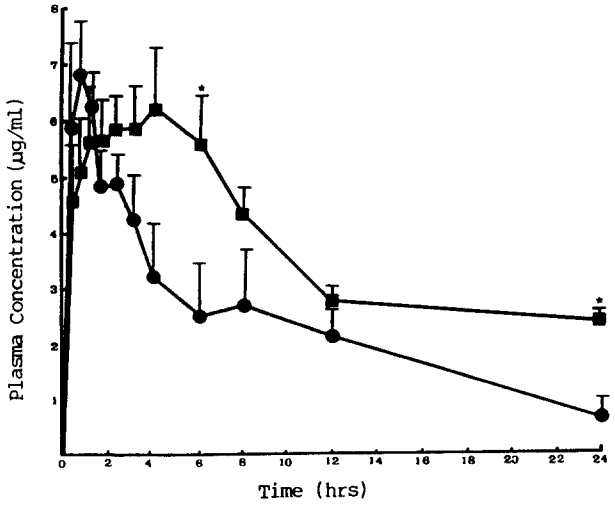

Fig. 9. Plasma concentration of naproxen after oral administration of 7 mg/kg to four rabbits. ●, naproxen; ■, microcapsules.
*$p<0.05$ between naproxen and microcapsules.

and MRT of microcapsules were significantly increased ($p<0.05$) and Cl/F was decreased compared with those of sodium naproxen powder. Therefore, it is concluded that sodium naproxen microcapsules coated with Eudragit RS can be used as a sustained release medication.

CONCLUSIONS

The present investigation on the microencapsulation of sodium naproxen with Eudragit RS showed the following results; The release of sodium naproxen was retarded by microencapsulation with Eudragit RS. The determination of CMC of Span 80 in solvent system is very important to produce the optimal concentration of Span 80 to prepare the smallest particles. The small particle size microcapsules bolonging to the powder

Table III. Pharmacokinetic parameters of naproxen and microcapsules after oral administration#

Dosage form	AUC^{0-24} [a] (μg min/ml)	MRT[b] (min)	Cl/F[c] (ml/min)
Naproxen	3529.00 ± 350.60	511.00 ± 32.0	2.04 ± 0.22
Microcapsule	5222.61*± 413.61	579.05*± 13.94	1.37*± 0.10

[a] AUC^{0-24} was calculated by trapezoidal method.
[b] MRT is $\frac{AUMC^{0-24}}{AUC^{0-24}}$
[c] Cl/F is the Dose/AUC^{0-24}.
*$p<0.05$ between naproxen and microcapsules.
#Mean± S.E. of four rabbits.

category were produced at the higher speed. The AUC and MRT of microcapsules were signficantly increased ($p<0.05$) and Cl/F was decreased compared with those of sodium naproxen powder.

ANKNOWLEDGEMENTS

This paper was supported in part by NON DIRECTED RESEARCH FUND, Korea Research Foundation, 1991.

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