Development of a Novel Drug Release System, Time-Controlled Explosion System (TES). II.[1] Design of Multiparticulate TES and *in Vitro* Drug Release Properties

Satoshi UEDA,*[,a] Hisami YAMAGUCHI,[b] Masateru KOTANI,[b] Sumihisa Kimura,[a] Yuji TOKUNAGA,[a] Akira KAGAYAMA,[b] and Takehisa HATA[a]

Pharmaceutical and Pharmacokinetic Research Laboratories,[a] Technological Development Laboratories,[b] Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan.
Received September 2, 1993; accepted October 22, 1993

For the design of multiparticulate Time-Controlled Explosion System (TES), the thickness of the swelling agent layer was optimized by determining the amount of drug released. Low-substituted hydroxypropylcellulose (L-HPC) was used as a swelling agent. At 120 μm thickness, tiapride hydrochloride was released before the membrane destruction, while at 180 μm thickness the drug release was completed within 30 min after the destruction. Similar results were obtained for TES containing metoclopramide hydrochloride. These results suggest that the L-HPC layer must be at least 180 μm thick. To evaluate the effect of solubility of the drug on release behavior, sodium diclofenac and nilvadipine were used as typical model drugs with an acidic functional group and poor solubility, respectively. The release studies were performed for these drugs in TES with 180 μm L-HPC layer. It is demonstrated that TES can provide a constant drug release profile, regardless of the solubility of a drug and dissolution conditions. In the case that L-HPC layer was fixed at a thickness of 180 μm, the release of diclofenac was not influenced by drug content.

Keywords time-controlled explosion system (TES); multiparticulate; swelling agent; solubility; drug release; lag time

We have recently been involved in developing a Time-Controlled Explosion System (TES) as a novel drug release system with a pre-designed lag time.[1] The spherical structure of TES consists of four laminar layers: from the center to outside, the core, drug layer, swelling agent layer and water insoluble polymer membrane. TES has a novel mechanism of drug release as described previously.[1] Briefly, water gradually penetrates the system through the outer membrane to expand the inner swelling agent. As soon as the swelling force of the hydrated swelling agent exceeds the tensile strength of the polymer membrane, destruction of the membrane is initiated. Drug release is triggered by the membrane destruction and the time until the destruction provides a lag time for the release. Lag time can also be freely controlled by changing the thickness of the outer membrane.

Theoretically, in this system any desired drug release can be achieved by the combination of TES with different lag times. From a practical point of view, however, TES must possess a size suitable for a multiparticulate dosage form. The ultimate size of TES is mainly determined by the core-size as well as thickness of the drug layer and the swelling agent layer.

Furthermore, the drug release from TES does not rely on pH of the outer milieu because the membrane destruction is not affected by pH.[1] It has not yet been clarified, however, whether the physicochemical properties of an incorporated drug influence the drug release of TES. In fact, in membrane-controlled diffusion systems, the drug release rate is affected by the solubility of the incorporated drug.[2]

The aim of this study was to clarify the feasibility of TES as a multiparticulate dosage form. For this purpose, the optimization of thickness of the swelling agent layer was performed using a sucrose seed, which has a diameter of 350 to 500 μm, as a core particle. Furthermore, the effect of the solubility on drug release was investigated using four different drugs: tiapride hydrochloride and metoclopramide hydrochloride as water soluble drugs, sodium diclofenac as a pH-dependent soluble drug, and nilvadipine as a poorly water soluble drug. The effect of drug content in TES on drug release was also examined by varying the amount of loaded drug.

Experimental

Materials Metoclopramide hydrochloride, tiapride hydrochloride (SEIF, Delagrange Pharmaceutical Co., FRG), sodium diclofenac (Yonezawa-Hamari Chemical Co., Ltd., Japan) and nilvadipine (Fujisawa Pharmaceutical Co., Japan) were used as model drugs. Low-substituted hydroxypropylcellulose (L-HPC® LH-31, Shin-etsu Chemical Co., Ltd., Japan), sucrose spheres [Nonpareil seed 103 grade (350—500 μm in diameter), Freund Industrial Co., Ltd., Japan], and ethylcellulose with a viscosity of 10 cP (EC, Ethocel®, Dow Chemical Co., MI) were used as a swelling agent, core particles and a membrane-forming agent, respectively. Hydroxypropylmethylcellulose (HPMC, TC-5R®, Shin-etsu Chemical Co., Ltd.) was used for a binder. HPMC was also used as a drug dispersing carrier for the solid dispersion matrix of nilvadipine. All the other chemicals were of analytical grade and used without further purification.

Drug Coating Pulverized active ingredients were coated on Nonpareil seeds while spraying 5% (w/v) ethyl alcohol–dichloromethane [8:2 (v/v)] of HPMC using a centrifugal granulator (model CF-360, Freund Industrial Co., Ltd.). In order to improve the solubility of nilvadipine, a solid dispersion was prepared according to the solvent method[3] by kneading lactose with nilvadipine and HPMC dissolved in ethyl alcohol–dichloromethane [8:2 (v/v)]. The solvent was evaporated to dryness in a vacuum oven heated at 40 °C. The pulverized solid dispersion powder was coated on Nonpareil seeds in a similar manner.

Coating of Swelling Agent and Membrane L-HPC passed through a 200 mesh screen (open size: 80 μm) was coated on the drug-coated spheres by a centrifugal granulator (model CF-360, Freund Industrial Co., Ltd.) as described previously.[1] The membrane coating was carried out using a fluid bed granulator (Flow-Coator Mini®, Freund Industrial Co., Ltd.) spraying 7% (w/v) EC solution dissolved in ethyl alcohol–dichloromethane [3:2 (v/v)] containing 10% (w/v) of suspended talc, as

described previously.[1)]

Drug Release Study and Membrane Destruction Study The dissolution studies were conducted by the JP XII paddle method at a rotation speed of 100 rpm, using 900 ml of JP XII 1st fluid (pH 1.2) and 2nd fluid (pH 6.8) maintained at 37±0.2 °C. In the case of nilvadipine, a 5 ml aliquot of sample solution was removed by a glass-syringe and then the same volume of fresh dissolution medium was restored. After filtration (0.22 μm Millipore® filter, type SJGV), an aliquot of the sample solution was diluted with methyl alcohol, and UV absorbance was measured at the wavelength of 254 nm (UV diode array spectrophotometer, type 8451A, Hewlett-Packard, PA). For the other three drugs, dissolution was monitored by an automatic dissolution test apparatus equipped with a UV system (UV diode array spectrophotometer, type 8451A, Hewlett-Packard, PA) at the wavelength of 254 nm.

Membrane destruction studies were carried out in the same manner. Two hundred TES particles were placed in 900 ml of JP XII 1st fluid or JP 2nd fluid prewarmed to 37 °C and stirred at the rotation speed of 100 rpm. The number of TES particles in which membrane destruction had initiated was visually counted every 30 min.

Each point represents the mean of five tests and the values of coefficient of variation were less than 5%.

Solubility of Drug Excess amounts of drugs were added to JP XII 1st fluid or 2nd fluid maintained at 37±0.2 °C and stirred by a magnetic stirrer. The solubility of each drug was measured for 24 h by monitoring UV absorbance in a similar way as done in the drug release study.

Measurement of Layer Thickness The duplicate measurement of particle size was performed by a profile projector (model V-16A, Nippon Kogaku K.K., Japan) on two dimensions of a particle. The thickness of the layer was calculated from the difference in the radius of the particle before and after coating. The obtained values of coefficient of variation for the particle size calculated from fifty samples were less than 6%.

Results

Solubility of Drugs Table I summarizes the solubilities of all the drugs used in this study in JP XII 1st fluid and 2nd fluid at 37°C.

Structure of TES Table II displays the formulations of metoclopramide-loaded TES particles with 120, 180 and 240 μm L-HPC layer thickness. The mean diameters of these TES particles are 840, 960 and 1080 μm, respectively.

A scanning electron micrograph of a cross-section of TES performed by scanning electron microscope (type S-650, Hitachi, Ltd.) is shown in Fig. 1. Multiparticulate TES used in this study was confirmed to have a spherical structure consisting of four laminar layers, *i.e.*, core particle (Nonpareil), drug (metoclopramide hydrochloride) layer, swelling agent (L-HPC) layer and water-insoluble polymer (EC) membrane, from center to outside.

Effect of Swelling Agent Amount on Drug Release Tiapride hydrochloride was used as a model drug since it exhibits almost the same solubility in JP 1st fluid (pH 1.2) and 2nd fluid (pH 6.8). To optimize the amount of swelling agent, two different TES with 120 and 180 μm L-HPC layers were prepared. The release profiles of tiapride from the TES are shown in Fig. 2. At the 120 μm L-HPC layer,

TABLE I. Solubility of Model Drugs in JP XII 1st Fluid (pH 1.2) and 2nd Fluid (pH 6.8) at 37 °C

Drug	Solubility (mg/ml)	
	1st fluid	2nd fluid
Tiapride hydrochloride	723	725
Metoclopramide hydrochloride	>200	17.6
Sodium diclofenac	1.4×10^{-3}	1.2
Nilvadipine	1.3×10^{-3}	1.1×10^{-3}

TABLE II. Formulation of Metoclopramide-Loaded TES[a)]

Function	Component	TES 1[b)]	TES 2[c)]	TES 3[d)]
Drug	Metoclopramide hydrochloride	8.0	8.0	8.0
Core	Sucrose beads	26.0	26.0	26.0
Swelling agent	L-HPC	37.0	55.0	73.0
Binding agent	HPMC	7.7	11.0	14.3
Membrane	Ethylcellulose	10.0	15.0	21.0
	Talc	1.0	1.5	2.1

a) Each component is represented as weight ratio (w/w). *b*) TES 1: mean diameter is about 840 μm. *c*) TES 2: about 960 μm. *d*) TES 3: about 1080 μm.

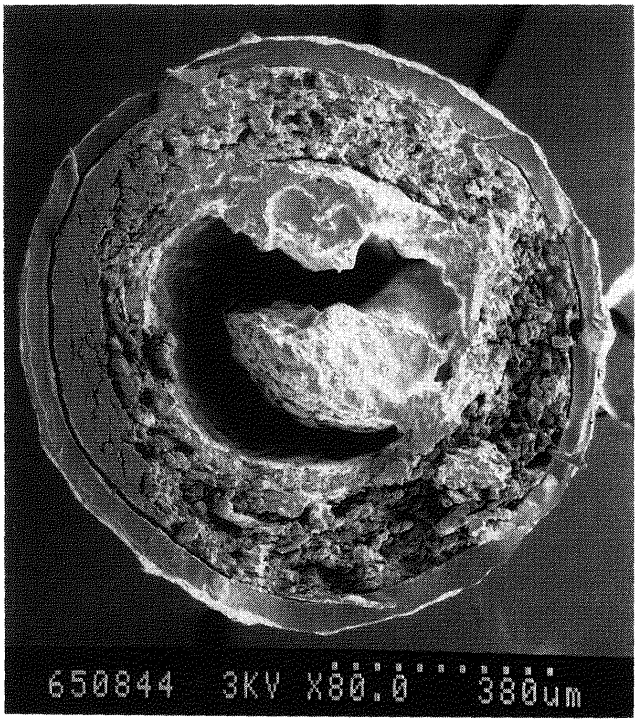

Fig. 1. Scanning Electron Micrograph of a Cross-Section of Multiparticulate TES

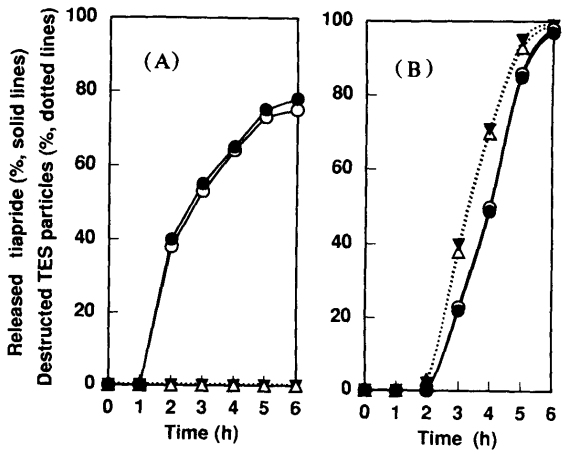

Fig. 2. Membrane Destruction Profiles of TES and Release Profiles of Tiapride from TES in JP XII 1st Fluid and 2nd Fluid

Membrane destruction: △, JP 1st fluid; ▼, JP 2nd fluid; drug release: ○, JP 1st fluid; ●, JP 2nd fluid. Mean thickness of L-HPC layer is 120 μm in (A) and 180 μm in (B). Mean thickness of EC membrane is 25 μm.

the release of tiapride was initiated after a lag time of 1 h, but membrane was not destroyed during the next 6 h [Fig. 2 (A)]. At the 180 μm L-HPC layer, in contrast, the destruction of the membrane was initiated after a lag time of 2 h and was completed within 6 h [Fig. 2(B)]. The release of the drug ran parallel to the membrane destruction, regardless of pH.

Three kinds of TES containing metoclopramide hydrochloride, which shows a higher solubility in the acidic region than in the neutral region, were prepared by changing the L-HPC amount. With TES with the 120 μm L-HPC layer, the membrane was not completely destroyed, that is, only a crack on the particle surface which was regarded as the beginning of destruction was observed. As shown in Fig. 3(A), the membrane was destroyed more rapidly at pH 6.8 than at pH 1.2. However, after the lag time, the release of metoclopramide was faster at pH 1.2 than at pH 6.8 due to its pH-dependent solubility. On the other hand, as shown in Figs. 3 (B) and (C), the system with more than the 180 μm L-HPC layer showed complete membrane destruction in both test solutions with pH-independent drug release. The release profiles of metoclopramide were almost the same as those of tiapride. Based on these results, the thickness of the swelling agent layer was fixed at 180 μm in the following studies.

Application of pH-Dependent Water Soluble Drugs to TES The release profiles of sodium diclofenac, which is poorly soluble in the acidic region, were examined and the results are shown in Fig. 4. There was no difference in release profile between JP XII 1st fluid and 2nd fluid.

Application of Poorly Water Soluble Drugs to TES As a model of a poorly water soluble drug, nilvadipine was incorporated in TES with the 180 μm L-HPC layer. Figure 5 shows the membrane destruction profile and the nilvadipine release profile of the TES. Complete membrane destruction was observed within 6 h after a lag time of 2 h. Nevertheless, nilvadipine showed almost the same solubility as diclofenac at pH 1.2 (TableI), although less than 50% of the drug was released during the same period. The retarded release is due to the slow dissolution rate of nilvadipine crystal. In order to improve the drug dissolution properties, the solid dispersion of nilvadipine using HPMC as a drug carrier was incorporated in TES.

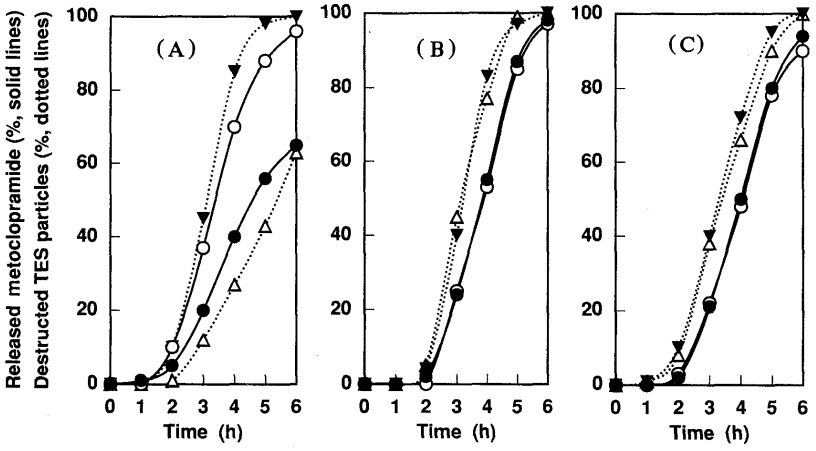

Fig. 3. Membrane Destruction Profiles of TES and Release Profiles of Metoclopramide from TES in JP XII 1st Fluid and 2nd Fluid

Membrane destruction: △, JP 1st fluid; ▼, JP 2nd fluid; drug release: ○, JP 1st fluid; ●, JP 2nd fluid. Mean thickness of L-HPC layer is 120 μm in (A), 180 μm in (B) and 240 μm in (C). Mean thickness of EC membrane is 25 μm.

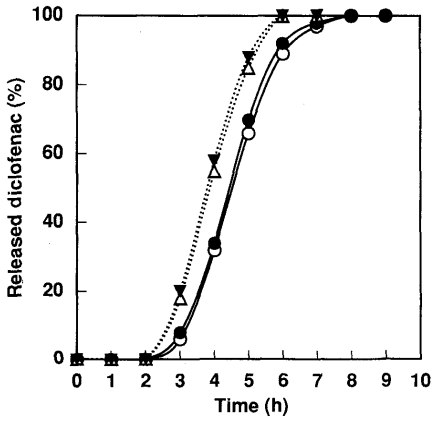

Fig. 4. Membrane Destruction Profiles of TES and Release Profiles of Diclofenac from TES in JP XII 1st Fluid and 2nd Fluid

Membrane destruction: △, JP 1st fluid; ▼, JP 2nd fluid; drug release: ○, JP 1st fluid; ●, 2nd fluid. TES particles containing 1.0 mg diclofenac were added to 900 ml of dissolution medium. Mean thicknesses of EC membrane and L-HPC layer are 25 and 180 μm, respectively. Diclofenac content is 7% (w/w).

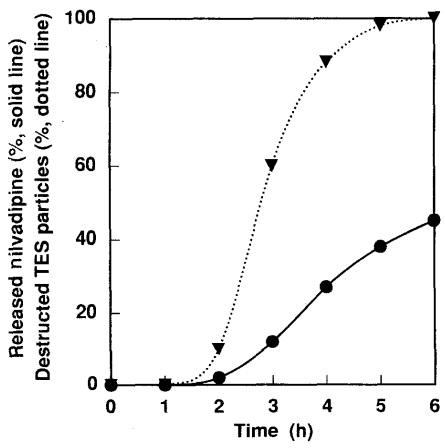

Fig. 5. Membrane Destruction Profiles of TES and Release Profiles of Nilvadipine (Used as Crystalline Drug) from TES in JP XII 2nd Fluid

Membrane destruction: ▼; drug release: ●. TES particles containing 0.5 mg nilvadipine were added to 900 ml of JP 2nd fluid. Mean thicknesses of EC membrane and L-HPC layer are 25 and 180 μm, respectively. Nilvadipine content is 7% (w/w).

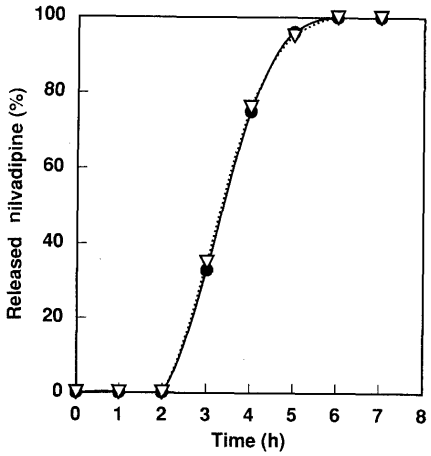

Fig. 6. Effect of Amount of Added Nilvadipine (Used as Solid Dispersion) on the Release Profile of TES in JP XII 2nd Fluid

Below saturation: —●— (TES particles containing 0.5 mg nilvadipine were added to 900 ml of JP 2nd fluid); super-saturated condition: ---▽--- (5 mg nilvadipine was added to 900 ml of JP 2nd fluid). Mean thicknesses of EC membrane and L-HPC layer are 25 and 180 μm, respectively. Nilvadipine content is 7% (w/w).

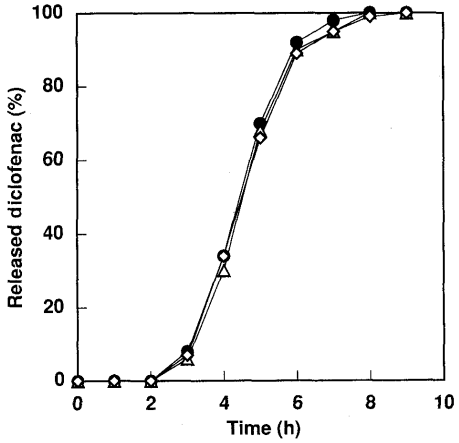

Fig. 7. Effect of Particle Size on the Release Profile of Diclofenac from TES in JP XII 2nd Fluid

Particle size: ●, 850—1000 μm [drug content = 7% (w/w)]; ◇, 1180—1400 μm [drug content = 25% (w/w)]; △, 1700—2000 μm [drug content = 45% (w/w)]. Mean thicknesses of EC membrane and L-HPC layer are 25 and 180 μm, respectively.

As shown in Fig. 6, the release profile obtained was similar to those of tiapride and metoclopramide. Furthermore, the drug was successfully released even in the super-saturated condition.

Effect of Particle Size and Drug Content on Drug Release By changing the thickness of the drug layer, three different TES particles were prepared. The final diclofenac content varied from 7% (w/w) to 45% (w/w) in proportion to the increased drug layer. As shown in Fig. 7, there was no difference in release profile among the preparations ranging from 850 μm to 2 mm in diameter.

Effect of EC Membrane on Drug Release The release of metoclopramide was investigated using TES with different membrane thicknesses ranging from 20 to 30 μm. The diameters of these TES particles were about 1 mm in size. As shown in Fig. 8, the initiation of the drug release was delayed with the increase in membrane thickness.

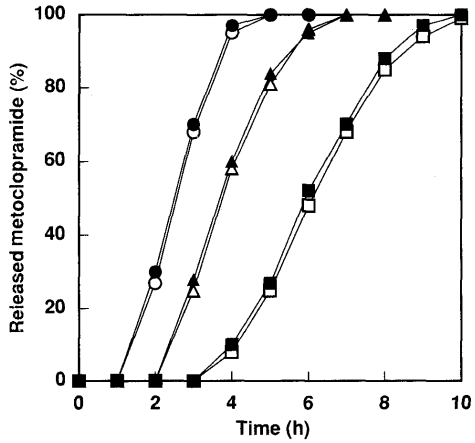

Fig. 8. Effect of EC Membrane Thickness on the Release Profile of Metoclopramide in JP XII 1st Fluid and 2nd Fluid

Test fluid: open key, JP 1st fluid; closed key, JP 2nd fluid; mean thickness of EC membrane: ○, ●, 20 μm; △, ▲, 25 μm; □, ■, 30 μm. Mean thickness of L-HPC layer is 180 μm.

Discussion

A number of sustained release or controlled release products are currently available for the treatment of various diseases. Depending on the physiological conditions, however, diffusion controlled devices cannot always provide a constant dissolution of biologically active drugs exhibiting pH-dependent solubility. Moreover, pH-dependent release of theophylline from retarded preparations is known to result in impaired bioavailability.[4] When a weakly basic drug, noscapine, is incorporated in a diffusion controlled system, precipitation may occur inside the system owing to elevation of the environmental pH during the gastrointestinal transit, and such precipitation can be avoided by the addition of organic acids.[5] Furthermore, the application of acidic drugs might provoke dose dumping in patients with anacidity if the dissolution is regulated by lower solubility at acidic pH. With regard to sustained release formulations, the measurement of pH-dependency of the *in vitro* dissolution is proposed to be a predictor of the *in vivo* bioavailability and the possible dose dumping effect.[6,7]

Recently, we have engaged in studies on TES. In this system, the swelling agent is crucial to the drug release mechanism.[1] The aim of this study is to clarify the feasibility of TES for control of drug release profiles independent of pH of the dissolution fluid. First, optimization of the thickness of the swelling agent (L-HPC) layer was performed. At the 120 μm L-HPC layer, the release of tiapride was not successfully controlled, that is, a typical diffusion controlled dissolution[2] was observed without destruction of the EC membrane [Fig. 2(A)]. Using TES loaded with metoclopramide, a slower release of the drug was observed in pH 6.8 compared with pH 1.2, due to the incomplete membrane destruction [Fig. 3(A)].

These phenomena might be explained as follows. Penetrated water in TES creates water channels in the L-HPC layer. If the L-HPC layer is thin, the penetrated water reaches the drug layer. Using the water thus created, the dissolved drug diffuses through membrane before it is

destroyed. It is believed that after drug release, a void space, which compensates the swelling force of hydrated L-HPC, is produced. As a result, the swelling force is not sufficient for membrane destruction.

Using TES with the 180 μm L-HPC layer, on the other hand, the membrane destruction controlled the release of both tiapride and metoclopramide [Figs. 2(B) and 3(B)]. There was no difference in release profile of metoclopramide between TES with the 180 and 240 μm L-HPC layers, and the pH-independent release was obtained even though metoclopramide displayed pH-dependent solubility [Figs. 3(B) and (C)]. The pH-independent release was also observed for the model acidic compound, sodium diclofenac (Fig. 4). Therefore, more than the 180 μm L-HPC layer is needed to prevent water penetration into the inner drug layer until the membrane destruction occurs.

Concerning poorly water soluble compounds, diffusion-controlled methods are not suitable for achieving sustained release owing to the slow dissolution of crystal. Control of dissolution can be achieved by regulating crystalline particle size.[8,9] When nilvadipine crystal was loaded into TES, the slow release was observed (Fig. 5). Whereas TES loaded with the solid dispersion of nilvadipine with HPMC produced release profiles similar to those of water soluble drugs (Fig. 6).

The effect of particle size on the drug release was assessed using sodium diclofenac as a model drug. TES particles from 850 μm to 2 mm in diameter were prepared by varying the drug layer thickness. When thickness of the L-HPC layer was fixed at 180 μm, the drug release was not altered by the particle size (Fig. 7), indicating that the drug release of TES is not influenced by the amount of drug loaded.

Our ultimate goal is the development of a system which can optionally control drug release; this can be achieved by combining TES particles possessing different lag times. In such a concept, lag time must be freely controlled. The outer membrane plays an important role not only in regulating of water penetration but also in maintaining of the shape. As seen in Fig. 8, the time necessary to initiate the release of metoclopramide was prolonged with increase of the membrane thickness. Therefore, the lag time of TES can be controlled by membrane thickness, even with a particle size of about 1 mm diameter.

In conclusion, TES has the potential to produce the desired release of various drugs independent of their physicochemical properties.

References

1) Part I: S. Ueda, T. Hata, S. Asakura, H. Yamaguchi, M. Kotani, Y. Ueda, *J. Drug Targeting*, in press, (1993).
2) G. Ragnarsson, A. Sandberg, M. O. Jhansson, B. Lindstedt, J. Sjogern, *Int. J. Pharm.*, **79**, 223 (1992).
3) W. L. Chiou, S. Riegelman, *J. Pharm. Sci.*, **60**, 1281 (1971).
4) D. Hellenbrecht, and C-D. Herzfeldt, *Med. Methods. Clin. Pharmacol.*, **7**, 67 (1987).
5) K. Thomas, T. Zimmer, *Int. J. Pharm.*, **58**, 197 (1990).
6) J. P. Skelly, L. A. Yamamoto, V. P. Shah, M. K. Yau, W. H. Barr, *Drug Dev. Indust. Pharm.*, **12**, 1159 (1986).
7) J. P. Skelly, M. Y. Yau, J. S. Elkins, L. A. Yamamoto, V. P. Shah, W. H. Barr, *Drug Dev. Indust. Pharm.*, **12**, 1177 (1986).
8) R. J. Hintz, K. C. Johnson, *Int. J. Pharm.*, **51**, 9 (1989).
9) E. K. Anderberg, C. Nystrom, *Int. J. Pharm.*, **62**, 143 (1990).