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A NEW TRANSMUCOSAL THERAPEUTIC SYSTEM : OVERVIEW OF FORMULATION DEVELOPMENT AND IN VITRO / IN VIVO CLINICAL PERFORMANCE

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ABSTRACT

A new transmucosal therapeutic system (TmTs) was developed for controlled systemic delivery of drugs, which are labile to hepatic "first-pass" metabolism, through oral mucosa. It consists of a fast-release

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layer, which provides a rapid release of drug for prompt rise in blood drug concentration to reach the therapeutic level, and a sustained-release layer, which releases the drug continuously for sustained duration to maintain the therapeutic level for up to 12 hrs. The sustained-release layer also contains mucoadhesive composition, so TmTs can be applied on gingival mucosa for continuous transmucosal controlled administration of drugs. Using isosorbide dinitrate (ISDN), a well-known antianginal drug which is known to be subjected to extensive presystemic elimination when taken orally, the systemic bioavailability has been improved by 37 fold in beagle dogs and by almost 5 fold in humans compared to that of marketed oral sustained-release tablet and the plasma concentration profile has also been prolonged to 12 hrs from less than 1 hr for marketed sublingual tablet and spray products in both beagle dogs and in human volunteers. Multi-fractional absorption model has been successfully applied for pharmacokinetic analysis, which demonstrates that the rate-limiting step for the transmucosal systemic delivery is the release of ISDN from the TmTs. Clinical studies performed in the anginal patients for up to one year have demonstrated the therapeutic benefits of this TmTs in achieving a substantial reduction in the frequency of anginal attacks and prolongation in the duration of exercise time.

INTRODUCTION

Organic nitrates have been used as the therapeutic agents for the treatment of angina pectoris for more than 100 years. Among these organic nitrates, nitroglycerin (NTG) and isosorbide dinitrate (ISDN) are still regarded as the therapeutic agents of first choice for the treatment and prevention of anginal attacks. NTG shows a rapid absorption and produces an immediate increase in its blood concentration following the sublingual administration, whereas only a negligible systemic bioavailability has been attained following oral administration ; this seems to be resulted from the extensive pre-systemic elimination of NTG. ISDN was first synthesized by Kranz et. al.[1], and has been demonstrated to exhibit a longer duration of antianginal activity than NTG and other organic nitrates. The manifestation of antianginal activity following the oral administration of ISDN has been well demonstrated[2]. However, the duration of the clinical effect of oral ISDN is only 3 - 4 hours, which is hence not sufficient long to meet the therapeutic needs[3-5]. For this reason, several oral sustained-release preparations of ISDN have been developed recently for clinical uses. However, ISDN, after oral administration, is also extensively metabolized by the

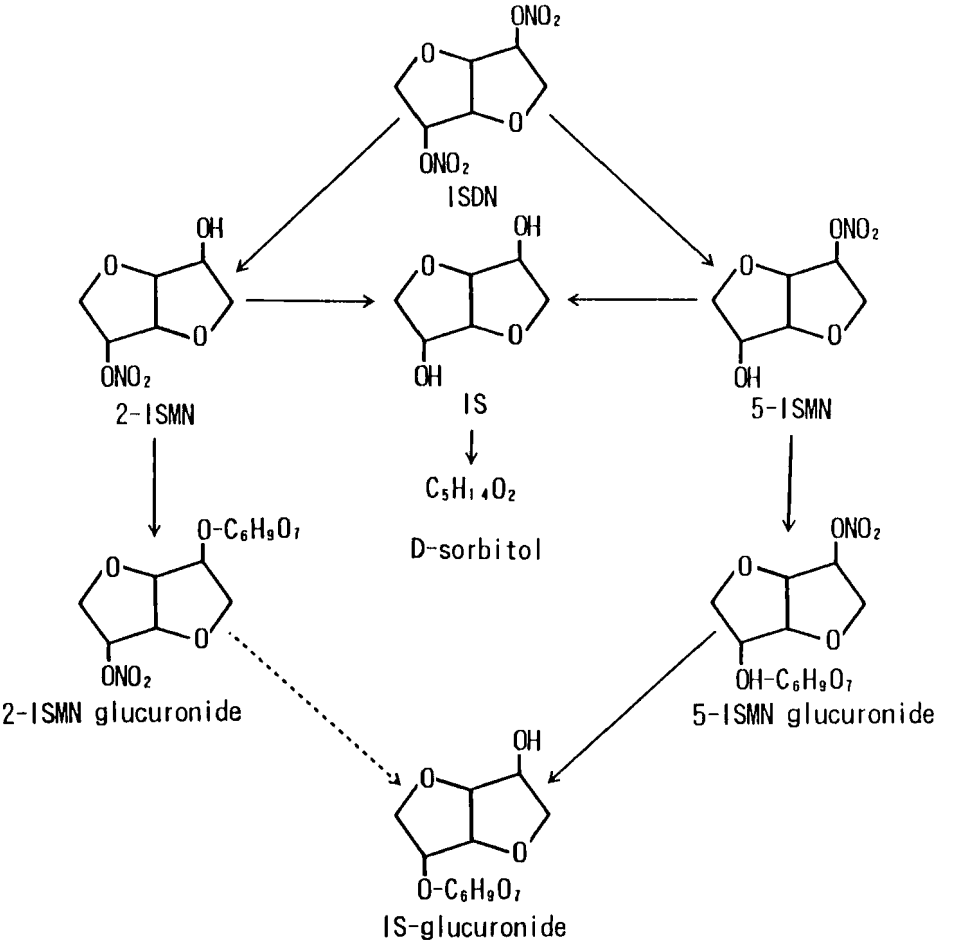


FIGURE 1
Metabolic pathway of isosorbide dinitrate(ISDN) keys : 2-ISMN(isosorbide-2-mononitrate), 5-ISMN(isosorbide-5-mononitrate), IS(isosorbide)

hepatic "first-pass" metabolism to form isosorbide-2-mononitrate (2-ISMN), isosorbide-5-mononitrate (5-ISMN) and other metabolites (Figure 1)[6,7]. Thus, the bioavailability of ISDN in human subjects has been reported to be as low as 22 - 29 %[8-10]

During the course of recent development in the field of pharmaceutical research, much efforts have been made to improve the shortcomings described above. In view of the potential of bypassing the hepatic "first-pass" metabolism associated with oral administration, non-parenteral routes of administrations, such as systemic delivery through the skin and the oral mucosa, have received increasing attention. Several skin patches, which achieve the transdermal systemic delivery of NTG or ISDN, have been recognized clinically to be an useful pharmaceutical preparations. Although a steady blood level is attained, without the hepatic "first-pass" metabolism, by the skin patch preparations, the problems, like the long delay in the onset of pharmacological effect due to the slow absorption of drug into systemic circulation at the beginning of patch application and the irritation and/or sensitization occurring at the application site have been reported[11-13].

The oral cavity is covered by a lining of oral mucosa, which, histologically, can be viewed as a bilayer membrane consisting of a stratified squamous epithelium on the surface and a connective tissue underneath. Similar to the skin, the oral mucosa acts, structurally and functionally, as the barrier to protect the vital organs underneath from the

surroundings. At the submucosa level, a rete venosum is well developed, via which a substance absorbed by the oral mucosa enters at first the jugular vein and finally pours into the systemic circulation. The substance, following oral mucosa absorption, thus avoids the hepatic "first-pass" metabolism. Therefore, oral mucosa has several advantages when it is used as the site for absorption. Among the oral mucosa, the gingival mucosa can be used as the platform for the holding of a drug delivery device designed for oral mucosa absorption. In view of the fact that oral cavity is also responsible for speaking, drinking and the ingestion of food, which requires mastication, so drugs that strongly hinder these functions will not be suitable for incorporation into the preparations designed for oral mucosa application. Thus, the preparations which exhibit the lowest potential of mucous irritation, the lowest effect on mouth activities, and is capable of releasing the drug continuously for a long period of time, after being applied to the mucosa, can be regarded as the ideal preparations for oral mucosa application.

The sublingual administration of ISDN via tablet and spray preparations has been a medical practice for decades. This route of administration permits the attainment of rapid absorption and immediate rise in

the blood level of ISDN, with the bypass of hepatic "first-pass" metabolism. It results in a rapid onset of antianginal effect, but its therapeutic efficacy lasts for a very short duration[3,14].

This article intends to provide an overview on the development of a novel transmucosal therapeutic system (TmTs) for the transmucosal controlled systemic delivery of drugs with extensive presystemic elimination, like ISDN, and the characterization of the pharmaceutics and pharmacokinetics of the transmucosal controlled delivery of drugs as well as their in vitro, in vivo and clinical performances.

DEVELOPMENT OF A TRANSMUCOSAL THERAPEUTIC SYSTEM

A transmucosal therapeutic system (TmTs) has been developed for long-term application, up to 12 hrs, to the oral mucosa. It is designed to release a therapeutic agent in the oral cavity at fast rate of dissolution at first and then continuously at sustained manner, aiming to achieve a systemic delivery as high and as rapidly as those obtained by sublingual administration, which makes a fast onset of clinical effect to be elicited ; furthermore, a sustained therapeutically-effective plasma level is maintained throughout the course of treatment.

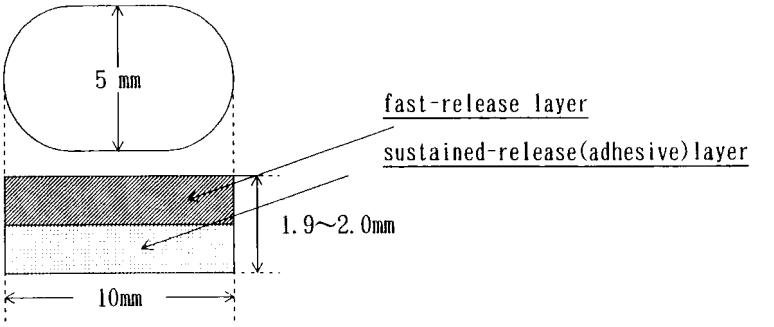


FIGURE 2
Physical structure and dimension of TYB-3215

As shown in Figure 2, TmTs is an track-field device and is designed for easy and comfortable application to the oral mucosa, especially to the gingival mucosa. It consists of 2 layers : the fast-release layer and the sustained-release layer. For prolonged adhesion to the gingiva surface, the sustained-release layer is formulated from a combination of mucoadhesive polymers.

In the case of transmucosal delivery of ISDN, which is designated as TYB-3215, distribution of an ISDN dose in the fast-release layer and in the sustained-release layer at the ratio of 1:4 was found to be at optimum. The fast-release layer contains mainly polyvinylpyrrolidone (PVP) and D-mannitol, which is designed to provide a fast-release of ISDN for rapid absorption and thus prompt rise in the blood concentration of ISDN to reach the therapeutically-

effective level. On the other hand, the sustained-release layer is composed mainly of PVP and polyacrylic acid, which becomes adhesive at first, upon uptake of water from saliva and then swelling to release ISDN at sustained release rate.

TYB-3215 has been found to have the following characteristics : 1) good adhesion to the oral mucosa, 2) very low local irritation and sense of foreign material, 3) formulation becomes gelling in the oral cavity after water absorption, 4) no, or little, hepatic "first-pass" metabolism, since ISDN permeates directly into the systemic circulation following the oral mucosa absorption, 5) possibility of promptly terminating the medication or any adverse effects, if necessary, by simply removing the TmTs from the oral cavity, 6) absence of any factors which usually affect G-I absorption, such as pH change and existence of foods in the digestive tract, the variation in gastric emptying time and intestinal passage time, and 7) feasibility of administering medication to the patients who can not take dosage forms orally.

DRUG RELEASE CHARACTERISTICS OF TmTs

Comparison with the Conventional ISDN Tablets

The comparative release profiles of ISDN from TYB-3215 and the conventional sublingual tablets of ISDN

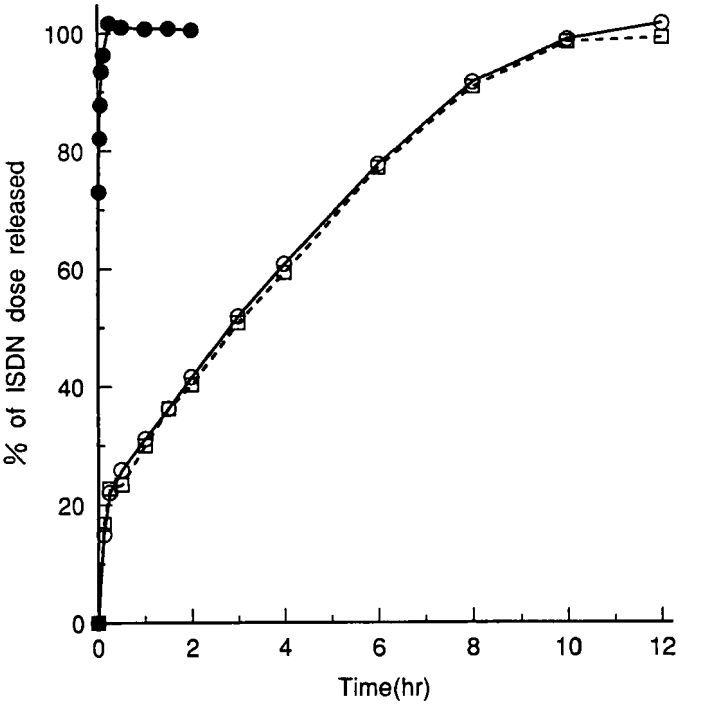


FIGURE 3
Comparative release profiles of ISDN from Nitrol® tablet(●, 5mg ISDN) and TYB-3215 (□, 5mg ; ○, 10mg ISDN) by dissolution test(paddle method, Japanese Pharmacopoeia, XII edition, n=6)

(Nitrol®), are shown in Figure 3. The results indicate that the sublingual tablet, which is often fabricated from an immediate-release formulation, releases ISDN very rapidly with its total loading dose dissoluted within approximately 15 min.

In comparison, TYB-3215 releases the fast-release fraction (20%) of the ISDN dose also within 15 min and then the sustained-release fraction (80%) continuously, but very slowly, over a course of 12 hr. It is

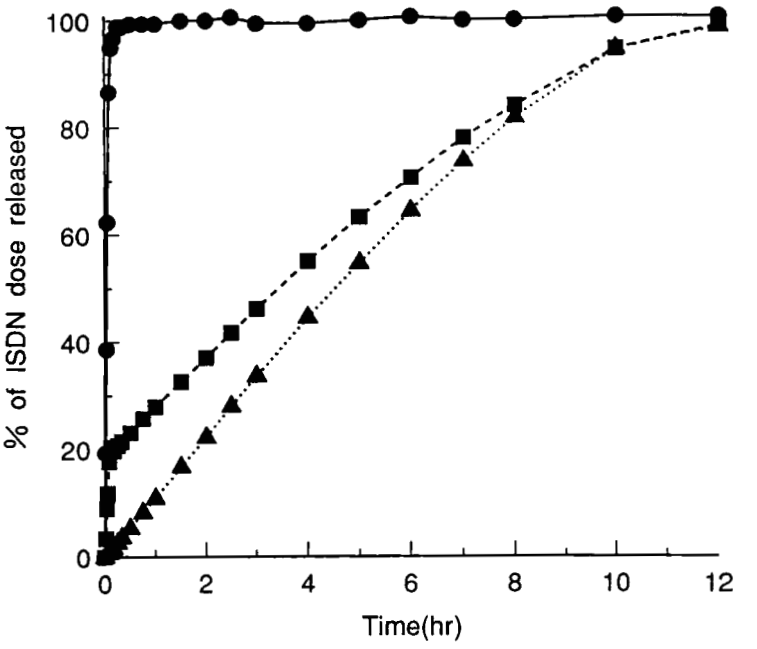


FIGURE 4
Release profiles of ISDN from TmTs formulations A (●), B (▲) and C (■) by dissolution test (Paddle method, Japanese Pharmacopoeia, XII edition, n=6)

encouraging to observe that there is no difference in the release pattern of ISDN from TYB-3215 between 5 mg and 10 mg dosage strengths.

Effects of Solution pH on the ISDN Release from TmTs

In order to evaluate the effect of pH variation in the oral fluid on the release kinetics of ISDN from TYB-3215. Dissolution kinetic studies were also per formed in solution with pH varying from 1.2 to 8.0. The dissolution profiles are compared in Figure 5,

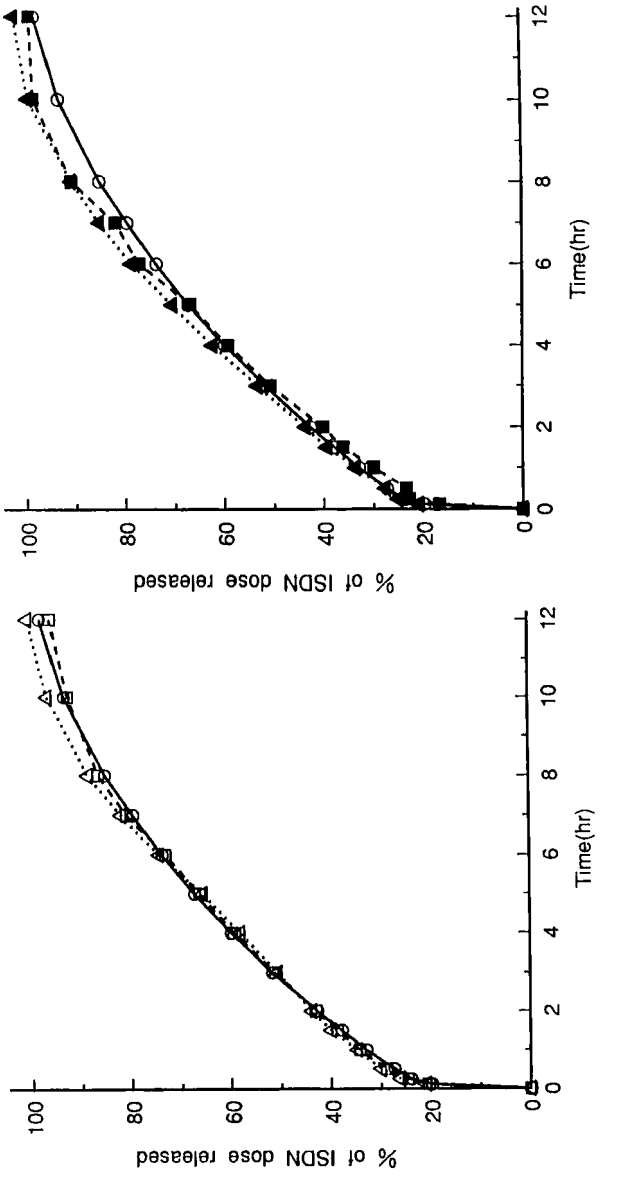


FIGURE 5
Effect of solution pH on the release profiles of ISDN from TYB-3215 (n=6)
Keys : (△) pH 1.2, (□) pH 4.0, (○) pH 6.0,
(■) pH 6.8, (▲) pH 8.0

which demonstrate that there is no difference in the release profile of ISDN in response to the variation in solution pH, even though polyacrylic acid, a component in the sustained-release layer, is known to be gelatinized only in the pH range of 6 - 9. However, as a result of poor gel formation in pH range of 1.2 - 4.0 ; some residues of the tablet were observed to remain in the dissolution medium even after 12 hr of dissolution.

The saliva is known to have a pH of approximately 7.0 under resting condition. As the salivary secretion increases, due to the physical and chemical stimuli (such as the mastication and gustation), the pH of the saliva tends to shift to the alkaline side. Also, the pH of the drink or food could cause some changes in oral pH, even though the residence time of the food in the oral cavity is normally not extremely long. Although the pH of the saliva varies the range of pH 6 - 8 upon the ingestion of the food, it is known to be returned to the original value, within 15 - 30 min, by the buffer action of the saliva. Therefore, the TmTs

Cumulative urinary and fecal excretion profiles of the radioactivity following the gingival application of ^{14}C-TYB-3215 are compared in Figure 7. The data appear to suggest that ISDN is excreted primarily through urinary excretion with the urinary radioactivity

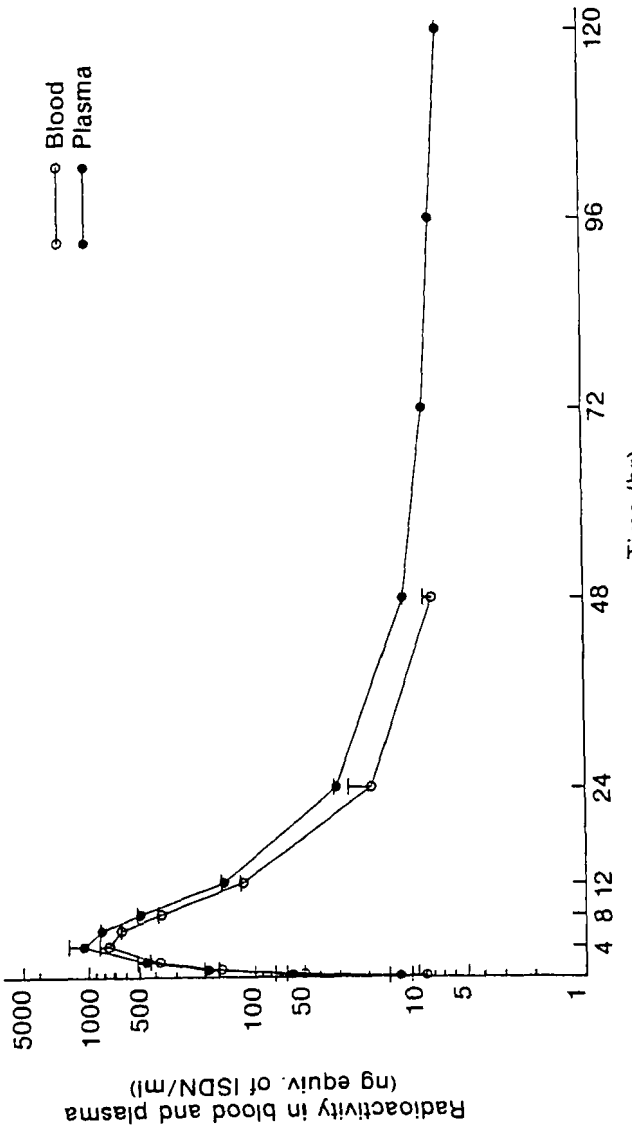


FIGURE 6
Radioactivity profile in the blood and plasma of non-fasting male dogs following the application of ^{14}C-TYB-3215 to the gingiva (dose : 10mg ISDN/100mg tablet of TYB-3215/animal). Data are expressed as the mean values (± S.E.) for three animals

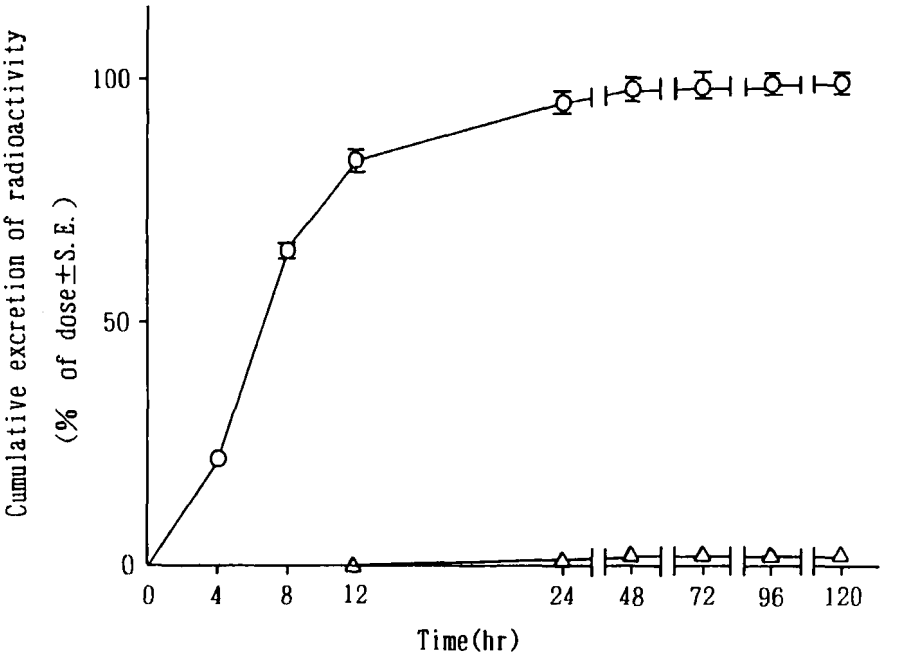


FIGURE 7
Cumulative excretion profiles of radioactivity in the urine and feces of non-fasting male dogs following application of ^{14}C-TYB-3215 to the gingiva (dose :10mg ISDN/100mg tablet of TYB-3215/animal)
keys : ○ urine, △ feces

reached 64.7% after 8 hr, 94.8% after 24 hr and 98.9% after 120 hr, respectively. On the other hand, only 2.2% of the radioactivity in the administered dose was excreted in the feces for a duration of up to 120 hr after administration. The results obtained demonstrate that ISDN is well absorbed after oral mucosa application of TYB-3215 and that the major route of excretion is via the urinary pathway.

applied to the gingival mucosa can be expected to be exposed to a solution at very much the neutral condition of pH 7.0 which is the mean value of resting pH, even though it may be exposed, for a very short time, to a condition beyond the pH range of 6-8[15-21]. Thus, the release profile of ISDN from TYB-3215 in the oral cavity can be expected not to be affected by the change in salivary pH.

PHARMACOKINETIC CHARACTERISTICS OF TmTs

Preclinical Studies in Beagle Dogs

1. Pharmacokinetics Following ^{14}C-labeled TmTs Administration

Following gingival application of TYB-3215, each contained 10mg of ISDN spiked with ^{14}C-ISDN, to each beagle dog, the plasma concentrations of the radioactivity was observed to reach the peak level at around 4 hr, and then decreased gradually thereafter (Figure 6). The amounts of radioactivity in the whole blood was found to be approximately 70% of that in the plasma[22].

The whole body autoradiograms (ARG) indicated that following the gingival application of ^{14}C-TYB-3215, a high radioactivity has been detected in the liver, kidney, mandibular gland and nasal cavity at 1 hr and 4 hr after administration, whereas the radioactivities in

other tissues and organs were approximately the same as that in the blood, and then decreased gradually with the time (Figure 8). In view of the possibility that a fraction of ISDN dose could be swallowed with the saliva, and absorbed from the gastrointestinal tract, ARG were also prepared from the animals with esophageal ligation and compared with those prepared from the animals without ligation. Although a higher radioactivity was observed in the oral cavity and the cervical part of the esophagus in the ligated animals than in the normal animals (Figure 9), the urine (in the bladder) and other tissues showed existence of an appreciable amount of the radioactivity, demonstrating that ISDN has been effectively absorbed from the oral mucosa of both the ligated and normal animals.

Contribution of the Fast- and Sustained-release Layer to the Release of ISDN

To evaluate the relative contribution of the fast-release layer and the sustained-release layer in TmTs on the drug release profile, the dissolution kinetics studies were performed on 3 different formulations : Formulation A, which contains 2 mg of ISDN (20% of the dosage strength) only in the fast-release layer, Formulation B, which contains 8 mg of ISDN (80% of the

dosage strength) only in the sustained-release layer, and Formulation C, which contains 2 mg of ISDN in the fast-release layer with another 8 mg of ISDN in the sustained-release layer (totally, 100% of the dosage strength). The release profiles of ISDN from these formulations are compared in Figure 4, which show that Formulation A, which contains ISDN only in the fast-release layer, has accomplished a total release of ISDN dose in less than 30 min, while Formulation B, which contains ISDN only in the sustained-release layer has produced a continuous and gradual release of ISDN over a duration of 12 hr. The release profile of ISDN from Formulation C suggests that the fast-release layer contributes to the initial release of ISDN, while the sustained-release layer achieves the continuous release of ISDN from TYB-3215.

2. Absorption of ISDN from Oral Mucosa and Pharmacokinetics Analysis

The plasma profiles of ISDN following the oral mucosa delivery of ISDN from 3 TmTs formulations are compared in Figure 10[23]. For comparison, two marketed products : a spray formulation (Nitrol® spray) and an i.v. injection formulation (Nitrol® inj.) were also conducted in beagle dogs (Figure 11).

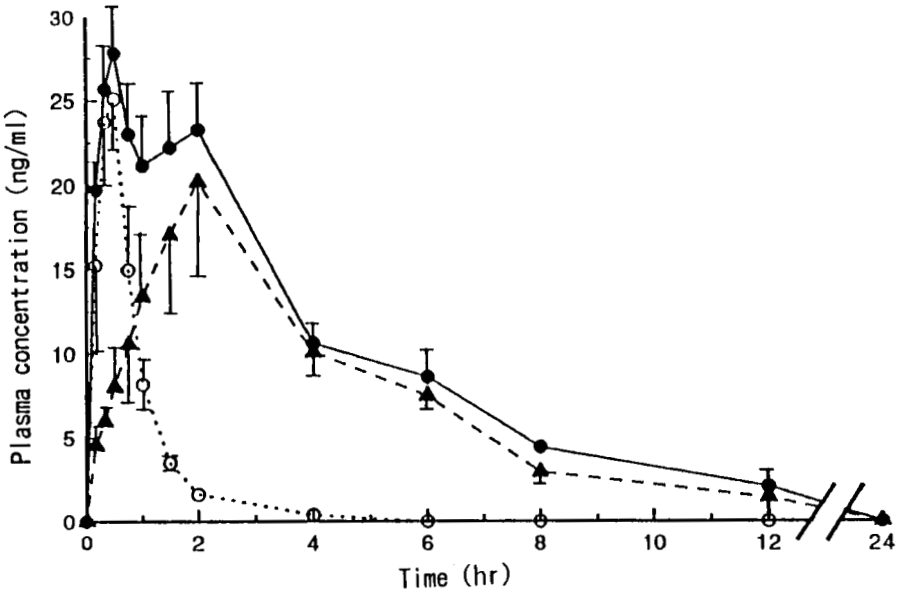


FIGURE 10
Plasma concentration (mean±S.E.) profiles of ISDN after gingival application of three TmTs formulations in beagle dogs (n=4) Keys : (○) : formulation (A), which contains 2 mg of ISDN only in the fast-release layer, (▲) : formulation (B), which contains 8 mg of ISDN only in the sustained-release layer, (●) : formulation (C), which containes 2 mg of ISDN in the fast-release layer and 8 mg of ISDN in the sustained-release layer.

The oral mucosa absorption profiles of ISDN, calculated by Loo-Riegelman analysis of these plasma profiles, from these formulations are compared in Figure 12. The results indicate that the absorption of ISDN from the oral mucosa, following the spray administration, is extremely rapid, more than 90% of the administered dose have be absorbed in less than 20 min after administration. In comparison, the TmTs Formulation A, which contains ISDN only in the fast-

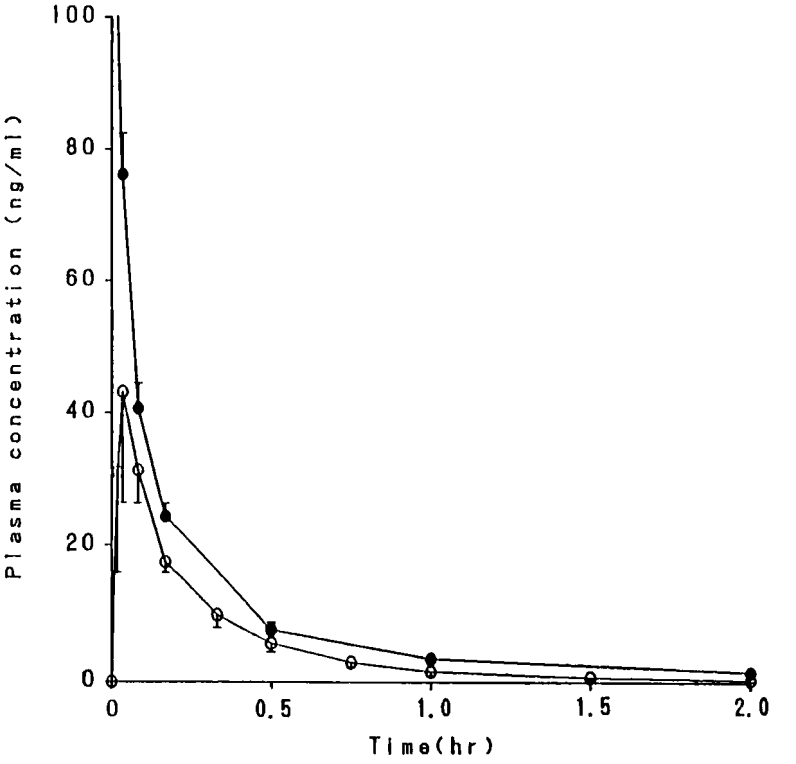


FIGURE 11
Plasma concentration (mean±S.E.) profiles of ISDN after i.v. administratin of Nitrol® injection (ISDN, 100 μg/kg) (●) and oral mucosa delivery of Nitrol® spray (ISDN, 1.25mg/animal) (○) in beagle dogs (n=4)

release layer, also exhibits a relatively rapid absorption of ISDN with greater than 80% of the dose absorbed within 1 hr after administration, while the absorption of ISDN from the Formulation B, which contains ISDN only in the sustained-release layer, is very slow and has attained 50% at around 5 hr and 90% at around 12 hr after administration. A continuous absorption over a long period has also been noticed.

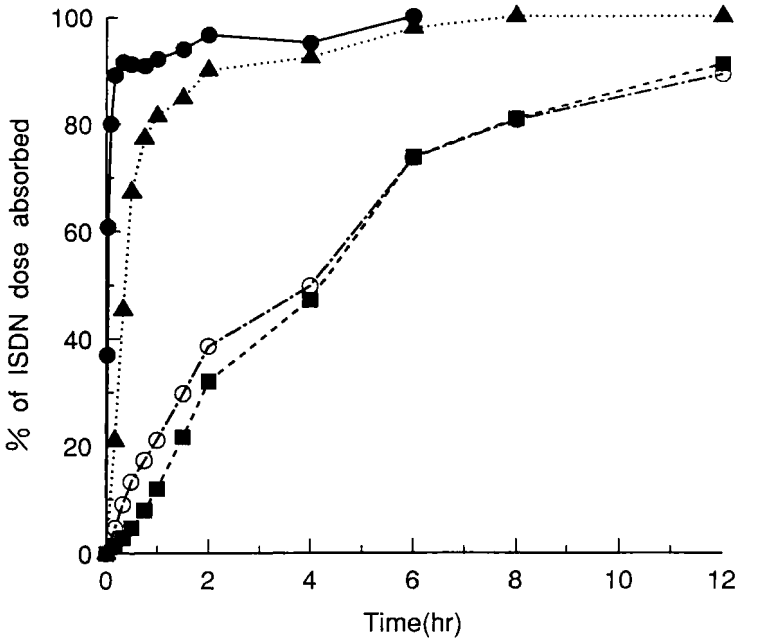
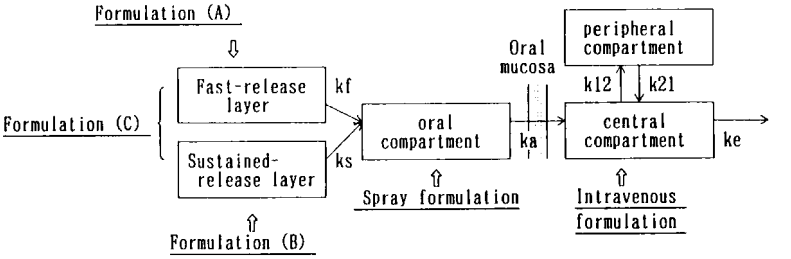


FIGURE 12
Absorption profiles of ISDN following the oral mucosa administration of ISDN from spray (Nitrol® spray) and TmTs formulations (A), (B) and (C) in beagle dogs (n=4)
Keys : (—●—) : spray formulation, (···▲···) : formulation (A), (--■--) : formulation (B), (---○---) : formulation (C)

After administration of the Formulation C, which contains ISDN in both the fast-release layer (20%) and the sustained-release layer (80%), the absorption profile in Figure 12 indicates that the absorption of ISDN is higher than that of the Formulation B in the first 4-hr period after administration, due to the absorption of additional ISDN delivered from the fast-release layer. Thereafter, however, there appears no difference in the absorption profiles between the

Formulation B and the Formulation C. These results demonstrate that the rate-limiting step in the oral mucosa absorption of ISDN from the TmTs formulation (TYB-3215) is in its release from the TmTs preparations. Therefore, the plasma concentration profile of ISDN can be controlled by adjusting the dissolution rate of ISDN from the TmTs preparation in the oral cavity.

The plasma concentration profiles (Figure 10) as well as the cumulative absorption profiles of ISDN (Figure 12) demonstrated that the fast-release layer contributes to the rapid absorption of ISDN and so the pharmacologically-effective plasma level can be attained immediately and also sustained for long period of time by the continuous release of ISDN from the sustained-release layer. The bioavailabilities of ISDN from the spray formulation and the TmTs formulation A, B and C were calculated to be 51, 67, 73 and 78%, respectively, when the i.v. formulation was used as the reference (which is known to achieve a bioavailability of 100%). Thus, the results appear to suggest that the formulations with fast rate of release tend to achieve a lower level of bioavailability (e.g., 51% for spray formulation). This could be attributed to the possibility that the formulation with faster rate of dissolution and thus the faster release of ISDN (e.g.,



The plasma profile (Cp) after :

(1) Intravenouse administration

$$Cp=\frac{Div}{Vc}\left\{\frac{k21-\alpha}{\beta-\alpha}e^{-\alpha t}+\frac{k21-\beta}{\alpha-\beta}e^{-\beta t}\right\} \quad (1)$$

(2) Spray administration

$0< t \leq tsp \quad Cp=0$

$tsp< t \quad Cp=Cp1$

$$Cp1=\frac{Dsp\,Fsp\,ka}{Vc}\left\{\frac{k21-\alpha}{(\beta-\alpha)(ka-\alpha)}e^{-\alpha t1}+\frac{k21-\beta}{(\alpha-\beta)(ka-\beta)}e^{-\beta t1}+\frac{k21-ka}{(\alpha-ka)(\beta-ka)}e^{-ka\,t1}\right\} \quad (2)$$

(3) Formulation (A) (ISDN is contained only in fast-release layer)

$0< t \leq tf \quad Cp=0$

$tf< t \quad Cp=Cp2$

$$Cp2=\frac{Df\,Ffkf\,ka}{Vc}\left\{\frac{k21-\alpha}{(\beta-\alpha)(ka-\alpha)(kf-\alpha)}e^{-\alpha t2}+\frac{k21-\beta}{(\alpha-\beta)(ka-\beta)(kf-\beta)}e^{-\beta t2}+\frac{k21-ka}{(\alpha-\beta)(\beta-ka)(kf-ka)}e^{-ka\,t2}+\frac{k21-kf}{(\alpha-kf)(\beta-kf)(ka-kf)}e^{-kf\,t2}\right\} \quad (3)$$

(4) Formulation (B) (ISDN is contained only in sustained-release layer)

$0< t \leq ts \quad Cp=0$

$ts< t \quad Cp=Cp3$

$$Cp3=\frac{Ds\,Fsks\,ka}{Vc}\left\{\frac{k21-\alpha}{(\beta-\alpha)(ka-\alpha)(ks-\alpha)}e^{-\alpha t3}+\frac{k21-\beta}{(\alpha-\beta)(ka-\beta)(ks-\beta)}e^{-\beta t3}+\frac{k21-ka}{(\alpha-\beta)(\beta-ka)(ks-ka)}e^{-ka\,t3}+\frac{k21-ka}{(\alpha-ks)(\beta-ks)(ka-ks)}e^{-ka\,t3}\right\} \quad (4)$$

(5) Formulation (C) (ISDN is contained in both fast- and sustained-release layers)

$0< t \leq tf \quad Cp=0$

$tf< t \leq ts \quad Cp=Cp2$

$ts< t \quad Cp=Cp2+Cp3$

Cp, Cp1, Cp2, Cp3 : Plasma concentration of ISDN (ng/ml) t : time (hr)
kf : first-order rate constant of release from fast-release layer(/hr)
ks : first-order rate constant of release from snstained-release layer(/hr)
ka : first-order rate constant for absorption (/hr)
k12: first-order rate constant for distribution from plasma to tissue (/hr)
k21: first-order rate constant for distribution from tissue to plasma (/hr)
Vc : volume of the central compartment (ml)
Div: dose of intravenous administration (ng)
Dsp: dose of spray administration (ng)
Df : dose of fast-release layer (ng)
Ds : dose of sustained-release layer (ng)
Fsp: fraction of dose from spray administration (%)
Ff : fraction of dose from fast-release layer (%)
Fs : fraction of dose from sustained-release layer (%)
tsp: lag time for spray administration (hr, t1=t-tsp)
tf : lag time for fast-release layer (hr, t2=t-tf)
ts : lag time for sustained-release layer (hr, t3=t-ts)

Scheme 1

TmTs formulation A) results in a shorter residence time of ISDN in the oral cavity which consequently results in a higher amount of ISDN being swallowed into the G.I. tract. The plasma profiles of ISDN in Figures 10 and 11 can be analyzed using the compartment model shown in Scheme 1 with various pharmacokinetic expressions for i.v. and oral mucosa absorption from the spray and TmTs formulations[23]. The agreement of the experimental data with the theoretical plasma profiles is compared in Figures 13 and 14 and pharmacokinetic parameters calculated are listed in Table 1. It is encouraged to observe that a good agreement between the experimental data and the simulation curve has been attained, which suggests that the plasma profiles of ISDN following the oral mucosa delivery of TYB-3215 fit well with this compartmental model. The plasma half-lives of ISDN determined are 1.94 min for α-phase and 23.10 min for β-phase, respectively. The first-order rate constant for the oral mucosa absorption of ISDN was calculated to be 47.56 hr^{-1} (or 0.793 min^{-1}), demonstrating that the absorption of ISDN from the oral mucosa is exremely rapid (with a half-life of only 0.87 min.).

3. Systemic Bioavailability and Metabolite of ISDN Following Oral Mucosa Absorption from TmTs in

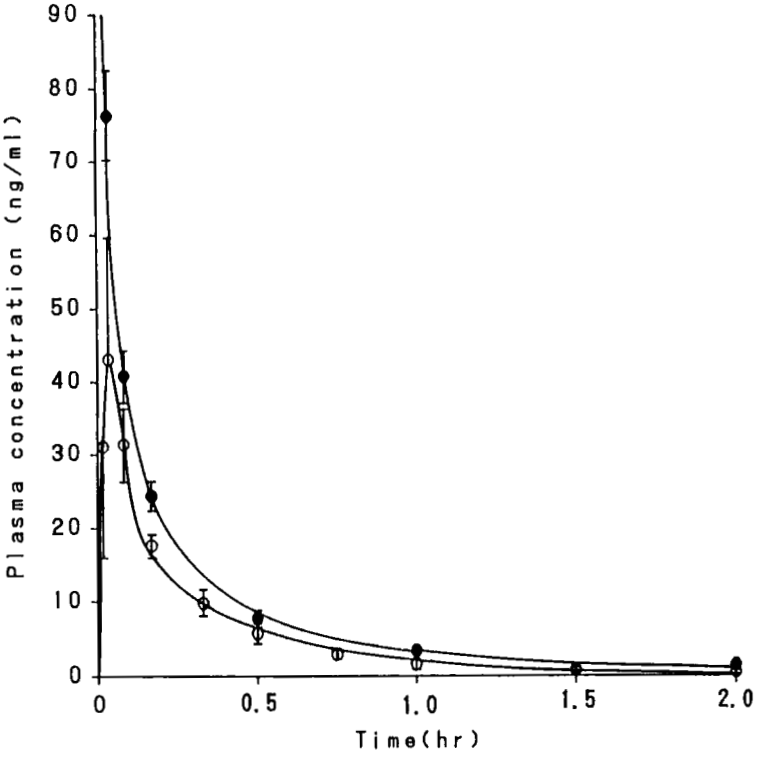


FIGURE 13
Plasma concentration (mean±S.E.) profiles of ISDN following i.v. injection and oral mucosa delivery of ISDN from spray formulation in beagle dogs (n=4) Keys : (●) i.v. administration, (○) spray administration
Where ● and ○ represent the experimental measurements and lines represent the simulated curves.

Comparison with Oral Sustained-release Tablets

The plasma concentration profiles of ISDN, and its two active metabolites, 2-ISMN and 5-ISMN, following the oral mucosa absorption of ISDN from TYB-3215, with 3 dosage strengths, are compared with the peroral administration of ISDN from the oral sustained-release tablets (Frandol®, 20 mg/tablet x 4 tablets = ISDN 80

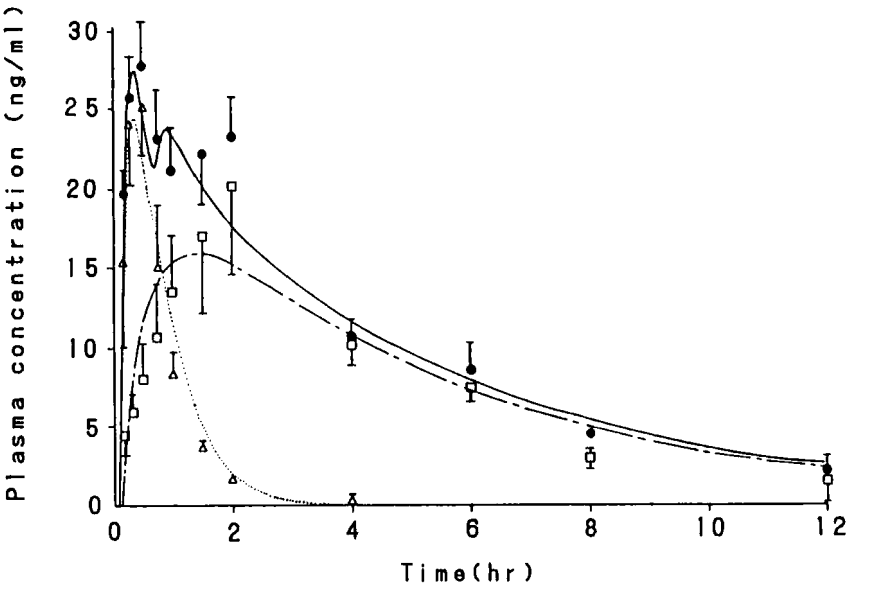


FIGURE 14
Plasma concentration (mean±S.E.) profiles of ISDN after oral mucosa delivery of ISDN from TmTs formulation (A), (B) and (C) in beagle dogs (n=4) Keys : (△) Formulation (A), (□) Formulation (B), (●) Formulation (C)
Where ●, △ and □ represent the experimental measurements and lines represent the simulated curves.

mg) in seven beagle dogs are shown, respectively, in Figures 15 - 17 ; and, the pharmacokinetic parameters are listed in Table 2[24]. The results in Figure 15 indicate that following oral mucosa absorption, ISDN reaches the peak levels (Cmax) within 1.4 - 2.6 hr and decreases gradually thereafter. The Cmax value after administration of TYB-3215 of lowest strength (2.5 mg/tablet) is 1.4 fold of that attained by the oral sustained-release (Frandol®) tablets with ISDN dose of

TABLE 1
Pharmacokinetic parameters for ISDN calculated by multi-line fitting

Parameter	Calculated value
$t_{1/2}\alpha$ (min)	1.94
$t_{1/2}\beta$ (min)	23.10
k12 (/hr)	10.79
k21 (/hr)	6.10
ke (/hr)	6.33
ka (/hr)	47.56
Vc (ℓ)	9.36
kf (/hr)	3.75
ks (/hr)	0.19
Fsp (%)	56.75
F_A (%)	67.97
F_B (%)	79.52
tsp (hr)	0.004
tf (hr)	0.09
ts (hr)	0.68
$AUC_{i.v.}$ (ng/ml•hr)[1]	21.37
AUC_{spray} (ng/ml•hr)[1]	11.28(F 50.98%[2])
AUC_A (ng/ml•hr)[1]	23.10(F 66.58%[2])
AUC_B (ng/ml•hr)[1]	100.46(F 72.88%[2])
AUC_C (ng/ml•hr)[1]	135.77(F 78.23%[2])
$MRT_{i.v.}$ (hr)	0.44
MRT_{spray} (hr)	0.46
MRT_A (hr)	0.73
MRT_B (hr)	5.72
MAT[3] (hr)	0.02
MDT_A[4] (hr)	0.27
MDT_B[5] (hr)	5.26

[1] calculated by the trapezoidal rule from the mean plasma data
[2] calculated from the AUC values
[3] $MAT = MRT_{spray} - MRT_{i.v.}$
[4] $MDT_A = MRT_A - MRT_{spray}$
[5] $MDT_B = MRT_B - MRT_{spray}$

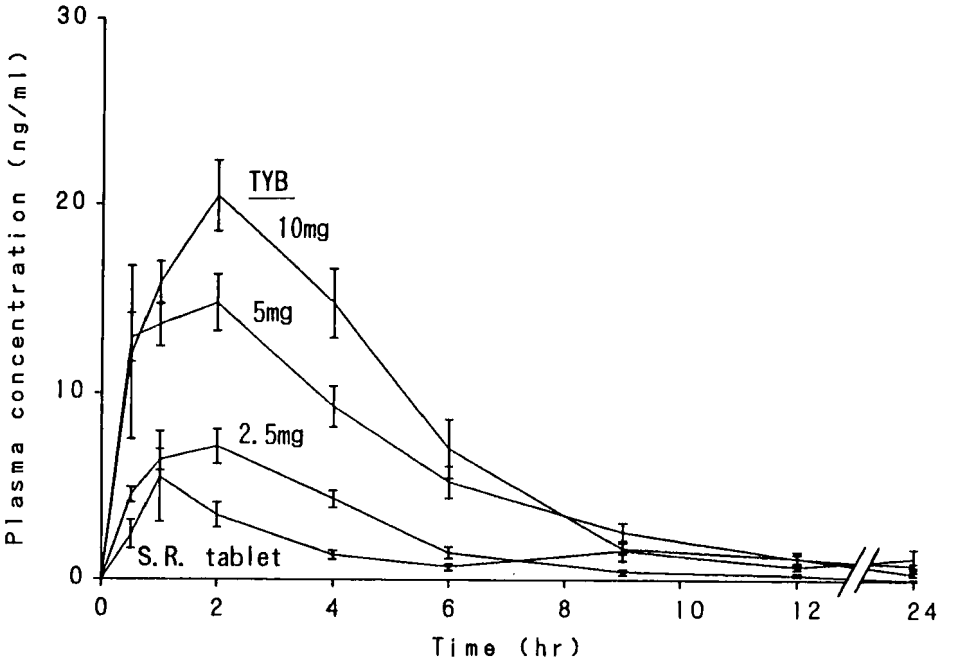


FIGURE 15
Plasma concentration (mean±S.E.) profiles of ISDN after the gingival application of TYB-3215, at varying doses, and oral sustained-release tablet (S.R., 20mg×4tab.) in beagle dogs (n=7)

32 times higher. The Cmax/D0 values achieved by TYB-3215 are 26.6 - 42.3 times greater than that by Frandol® tablets. The area under the plasma concentration-time curve per unit dose (AUC/D0) achieved by TYB-3215 is 28.5 - 47.3 times greater than that from the administration of oral sustained-release Frandol® tablets. Apparently, a better systemic bioavailability and a higher plasma level of ISDN has been achieved by the oral mucosa delivery of TYB-3215 than the peroral administration of sustained-release

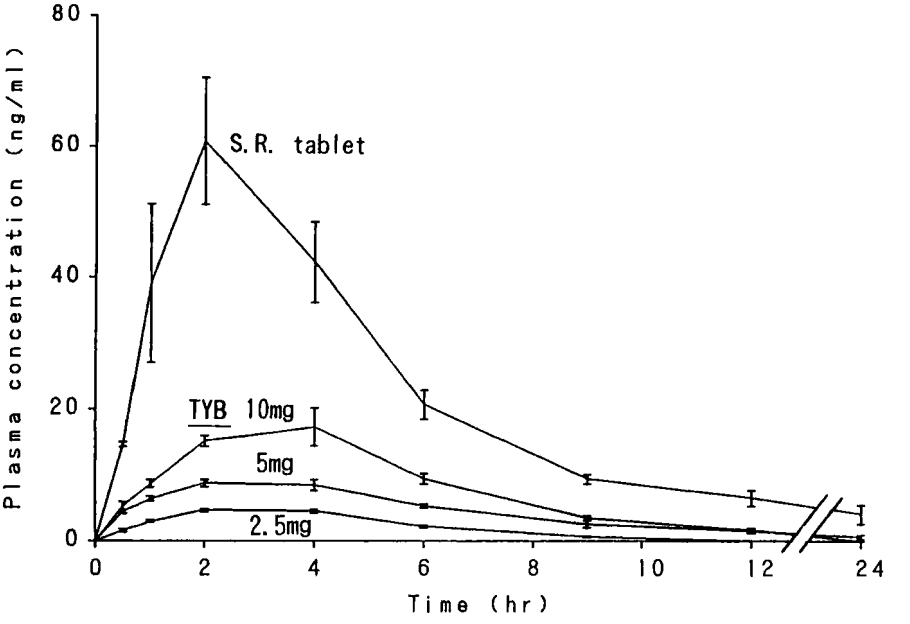


FIGURE 16
Plasma concentration (mean±S.E.) profiles of 2-ISMN after the gingival application of TYB-3215, at varying doses, and sustained-release tablet (S.R., 20mg×4tab.) in beagle dogs (n=7)

tablets. The difference appears to be attributed to the pre-systemic metabolism of ISDN to 2- and 5-ISMN.

The plasma profiles in Figures 16 and 17 suggest that 2-ISMN and 5-ISMN appear in the plasma slowly, which reach their respective peak levels at 3.1 - 3.4 hr and 3.4 - 4.0 hr, after administration and then decrease gradually thereafter. Compared to the plasma profiles of ISDN (Figure 15), the peroral administration of sustained-release tablets has produced higher plasma concentrations of 2-ISMN and 5-

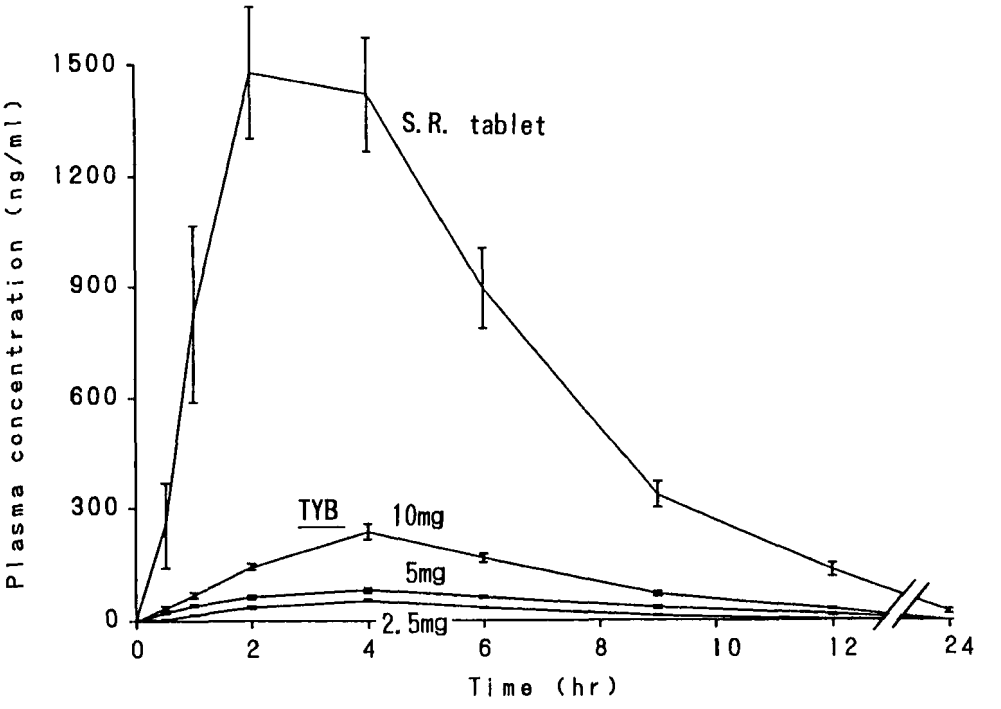


FIGURE 17
Plasma concentration (mean±S.E.) profiles of 5-ISMN after the gingival application of TYB-3215, at varying doses, and sustained-release tablet (S.R., 20mg×4tab.) in beagle dogs (n=7)

ISMN than those from the transmucosal delivery of ISDN by TYB-3215.

The Cmax ratios of 2-ISMN and 5-ISMN over ISDN are 0.6 - 0.8 and 5.0 -11.0, respectively, from the transmucosal delivery by TYB-3215 as compared to 10.8 and 282.1, respectively, from the peroral administration of Frandol® tablets. The AUC ratios of these metabolites over ISDN are 0.8 - 1.0 and 7.0 - 14.1, respectively, from the administration of TYB-3215

Table 2 Pharmacokinetic parameters of ISDN, 2-ISMN and 5-ISMN after dosing of TYB-3215 and sustained-release tablet in beagle dogs

	Cmax (ng/ml±SE)	Ratio [1]	Cmax/Do [2]	Tmax (hr±SE)	MRT (hr±SE)	AUC (0→24) (ng/ml・hr±SE)	Ratio [1]	AUC/Do
TYB-3215 (2.5mg ISDN)								
ISDN	8.1(±0.8)	1.0	3.24	1.8(±0.4)	3.5(±0.4)	35.4(± 2.5)	1.0	14.2
2-ISMN	5.0(±0.1)	0.6		3.1(±0.4)	4.3(±0.4)	26.8(± 1.5)	0.8	
5-ISMN	55.4(±3.8)	6.8		4.0(±0.0)	5.0(±0.3)	312.5(±20.4)	8.8	
TYB-3215 (5mg ISDN)								
ISDN	16.9(±1.3)	1.0	3.38	1.4(±0.2)	5.4(±0.2)	94.5(± 7.6)	1.0	18.9
2-ISMN	9.9(±0.8)	0.6		3.1(±0.4)	6.3(±0.7)	71.2(± 3.9)	0.8	
5-ISMN	84.0(±7.4)	5.0		3.4(±0.4)	5.9(±0.4)	657.1(±32.2)	7.0	
TYB-3215 (10mg ISDN)								
ISDN	21.3(±2.0)	1.0	2.13	2.6(±0.4)	4.6(±0.1)	114.1(± 9.6)	1.0	11.4
2-ISMN	17.2(±0.9)	0.8		3.4(±0.4)	5.1(±0.2)	111.3(± 5.5)	1.0	
5-ISMN	235.3(±24.0)	11.0		4.0(±0.0)	5.9(±0.1)	1605.6(±94.5)	14.1	
Oral S.R. tablet (80mg ISDN)								
ISDN	6.0(±2.3)	1.0	0.08	1.6(±0.2)	8.3(±1.2)	32.5(± 8.3)	1.0	0.4
2-ISMN	64.6(±10.3)	10.8		2.4(±0.4)	6.3(±0.7)	365.3(± 33.3)	11.2	
5-ISMN	1692.7(±154.8)	282.1		2.9(±0.4)	5.4(±0.3)	10188.3(±701.2)	313.5	

[1] means the ratio of metabolite over ISDN
[2] means the value per unit dose

as compared to 11.2 and 313.5, respectively, from the peroral administration of Frandol® tablets. Thus, transmucosal controlled systemic delivery of ISDN via oral mucosa has produced extremely smaller Cmax and AUC ratios of the metabolites over ISDN than those observed after the peroral administration of oral sustained-release tablets. Therefore, it was concluded that the pre-systemic metabolism of ISDN can be substantially minimized by transmucosal delivery by the gingival application of TYB-3215, leading to the higher bioavailability of ISDN with the reduced formation of metabolites.

Pharmacokinetics in Healthy Male Volunteers

1. Bioavailability and Metabolism of ISDN Folloeing Transmucosal Absorption from TmTs vs Oral Sustained-release Tablets

The plasma concentration profiles of ISDN and its two active metabolites, 2-ISMN and 5-ISMN, following the oral mucosa absorption of ISDN from TYB-3215, with 3 dosage strengths, are compared with the peroral administration of ISDN from a single sustained-release tablet (Frandol® tablet, ISDN : 20 mg) in eight healthy volunteers are shown, respectively, in Figures 18 - 20 and the pharmacokinetic parameters are listed in Table 3[25]. The results in Figure 18 indicate that

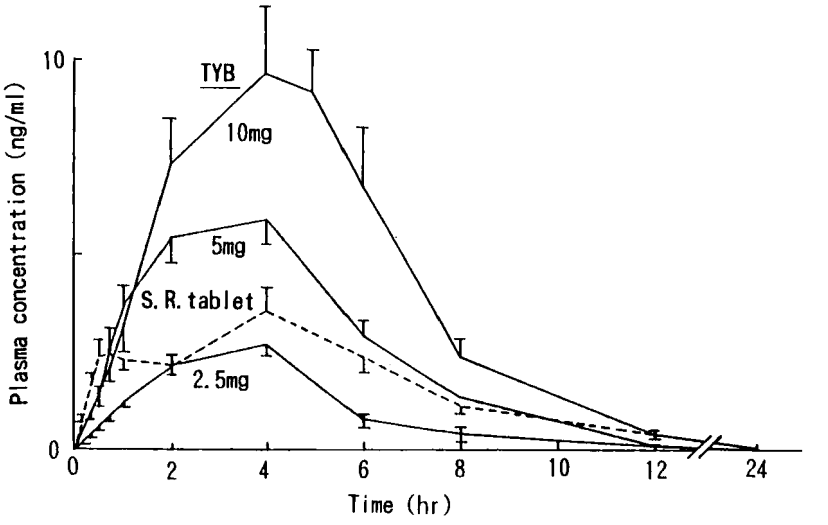


FIGURE 18
Plasma concentration (mean±S.E.) profiles of ISDN after the gingival application of TYB-3215, at varying doses, and oral sustained-release tablet (S.R., 20mg) in healthy male volunteers (n=8)

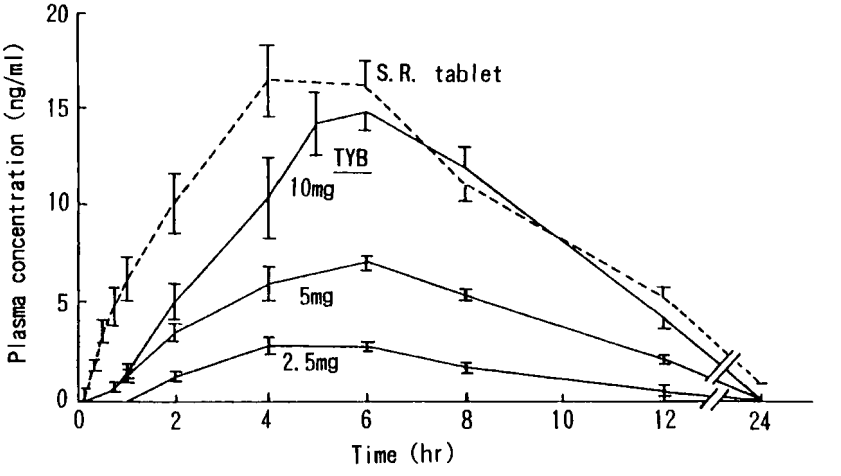


FIGURE 19
Plasma concentration (mean±S.E.) profiles of 2-ISMN after the gingival application of TYB-3215, at varying doses, and oral sustained-release tablet (S.R., 20mg) in healthy male volunteers (n=8)

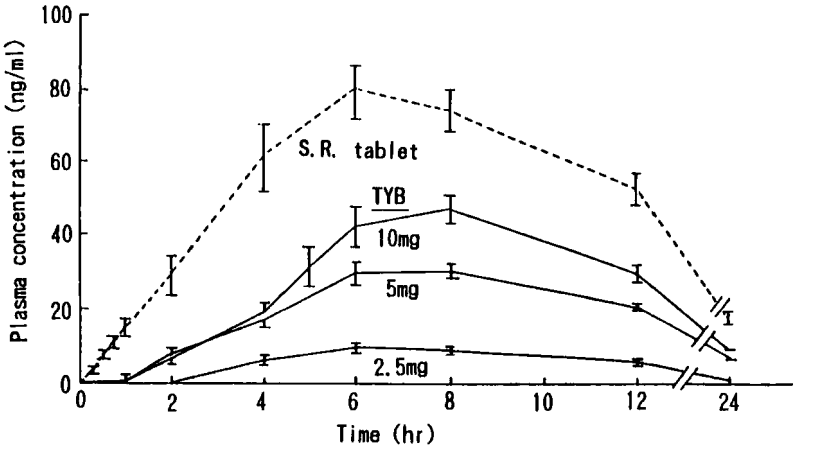


FIGURE 20
Plasma concentration (mean±S.E.) profiles of 5-ISMN after the gingival application of TYB-3215, at varying doses, and oral sustained-release tablet (S.R., 20mg) in healthy male volunteers (n=8)

following oral mucosa absorption, ISDN reaches Cmax within 0.5 - 4.0 hr after gingival application of TYB-3215 and then decreases gradually thereafter. The plasma concentrations of ISDN attained by the peroral administration of sustained-release tablets, which contain 20 mg of ISDN each, are between those achieved by the 2.5 mg and 5 mg tablets of TYB-3215. Apparently, the TYB-3215 has achieved a clinical bioavailability that is 4.4 - 5.4 times of that obtained by the oral sustained-release tablet. A good linear relationship has also been established between the Cmax values and the ISDN doses administered, and between the AUC values and the administered doses (Figure 21) ; and, the

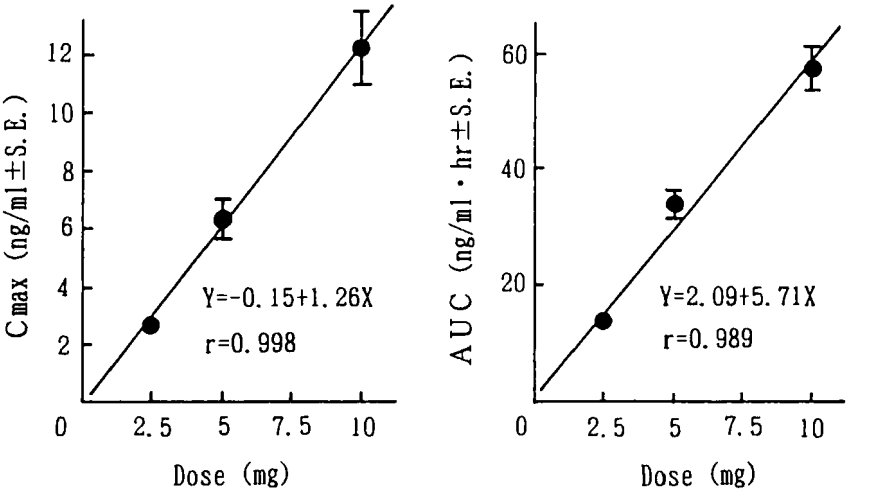


FIGURE 21
Linear relationship between the Cmax and the dose and between the AUC and the dose administered to healthy male volunteer (n=8)

dose-dependent increase of these pharmacokinetic parameters is thus demonstrated. On the other hand, no statistically significant difference has been observed in the time reaching Cmax (i.e., Tmax) and the mean residence time (MRT) among the 3 dosage strengths of TYB-3215. Therefore, the linear pharmacokinetics of ISDN has been shown to be maintained within this dosage range.

The appearance of 2-ISMN and 5-ISMN, the metabolites of ISDN, in the systemic circulation was found to be slightly slower from the transmucosal delivery by TYB-3215 than from the peroral administration by the sustained-release tablets (with

Tmax values of 5.3 - 5.8 hr and 6.5 - 7.3 hr, respectively, as compared to 5 and 6 hr). The ratios of 2-ISMN and 5-ISMN to ISDN were 1.1 - 1.3 and 3.4 - 4.9, respectively, in Cmax values and 1.5 - 2.3 and 7.1 - 13.1, respectively, in AUC values following transmucosal delivery by TYB-3215. These ratios are substantially smaller than the 4.3 and 19.0, respectively, in Cmax value and 6.8 and 50.2, respectively, in AUC value, following the peroral administration by sustained-release tablet. Thus, the hepatic "first-pass" metabolism of ISDN has also been avoided in humans, as shown earlier in the beagle dogs, by the transmucosal delivery via the gingival administration of TYB-3215.

Cumulative urinary excretion of ISDN and its metabolites during the 24-hr period following the gingival application of TYB-3215 and the peroral administration of sustained-release tablets are listed in Table 4. A total of 59.7 - 74.7% of the ISDN dose administered were excreted in the urine as the unchanged compound and its metabolites (2-ISMN, 5-ISMN and their conjugates and isosorbide) from the gingival application of TYB-3215, which is very much similar to the 62.8% by the peroral administration of sustained-release tablet. The results suggest that transmucosal delivery does not alter the pathways of excretion. The

Table 3 Pharmacokinetic parameters of ISDN, 2-ISMN and 5-ISMN after dosing of TYB-3215 and sustained-release tablet in human subjects

	Cmax (ng/ml±SE)	ratio[1]	Tmax (hr±SE)	MRT(hr±SE) 0-24	MRT(hr±SE) 0-∞	AUC (ng/ml·hr±SE) 0-24	ratio[1]	AUC (ng/ml·hr±SE) 0-∞	ratio[1]	Relative bio-availability[2]
TYB-3215 (2.5mg ISDN)										
ISDN	2.79(±0.25)	1.0	3.75(±0.25)	4.25(±0.43)	4.49(±0.62)	13.67(± 1.45)	1.0	13.88(± 1.62)	1.0	439
2-ISMN	3.15(±0.27)	1.1	5.25(±0.37)	6.23(±0.54)	6.23(±0.54)	20.99(± 2.40)	1.5	20.99(± 2.40)	1.5	
5-ISMN	9.56(±1.34)	3.4	6.50(±0.50)	9.06(±0.35)	9.91(±1.17)	96.35(±12.64)	7.0	99.05(± 11.93)	7.1	
TYB-3215 (5mg ISDN)										
ISDN	6.46(±0.74)	1.0	3.75(±0.70)	4.16(±0.27)	4.16(±0.27)	34.34(± 2.49)	1.0	34.34(± 2.49)	1.0	544
2-ISMN	7.42(±0.44)	1.1	5.75(±0.45)	7.24(±0.22)	7.24(±0.22)	64.27(± 2.83)	1.9	64.27(± 2.83)	1.9	
5-ISMN	31.55(±2.38)	4.9	6.75(±0.37)	10.31(±0.27)	13.26(±0.62)	392.13(±21.74)	11.4	449.17(± 25.02)	13.1	
TYB-3215 (10mg ISDN)										
ISDN	12.34(±1.31)	1.0	4.75(±0.31)	4.85(±0.31)	5.23(±0.47)	57.89(± 3.91)	1.0	57.92(± 3.92)	1.0	458
2-ISMN	16.43(±1.26)	1.3	5.63(±0.42)	7.48(±0.28)	7.49(±0.29)	131.07(± 8.63)	2.3	131.12(± 8.65)	2.3	
5-ISMN	50.83(±3.90)	4.1	7.25(±0.37)	10.27(±0.28)	12.61(±0.57)	545.31(±30.32)	9.4	609.28(± 36.12)	10.5	
Oral S.R. tablet(20mg ISDN)										
ISDN	4.32(±0.48)	1.0	3.20(±0.84)	5.54(±0.18)	6.03(±0.24)	24.78(± 1.68)	1.0	25.27(± 1.70)	1.0	100
2-ISMN	18.42(±1.58)	4.3	5.00(±0.38)	7.43(±0.24)	8.13(±0.48)	167.21(±10.29)	6.7	172.36(± 10.69)	6.8	
5-ISMN	82.06(±6.44)	19.0	6.00(±0.38)	9.97(±0.14)	13.86(±0.75)	1073.84(±90.26)	43.3	1269.65(±110.78)	50.2	

[1] the ratio of metabolite over ISDN

[2] Relative bioavailability(%)=AUC(TYB-3215/Dose)÷AUC (S.R. tablet/20)×100

TABLE 4
Cumulative urinary excretion of ISDN and metabolites in human subjects.

Trial Drug	Excrete	Cumulative urinary excretion (% of dose ±SE)[1] 0 ~ 6 hr	0 ~ 12 hr	0 ~ 24 hr
TYB-3215(2.5mg)	IS	4.51(±2.73)	23.19(±8.25)	42.75(±14.56)
	5-ISMN(Conjugate)	2.92(±0.35)	9.13(±0.59)	14.68(± 0.92)
	2-ISMN(Conjugate)	0.04(±0.02)	0.09(±0.03)	0.09(± 0.03)
	5-ISMN(Free)	0.36(±0.07)	1.19(±0.15)	2.02(± 0.22)
	2-ISMN(Free)	0.03(±0.01)	0.08(±0.01)	0.11(± 0.01)
	ISDN×10³	9.22(±1.48)	10.79(±1.43)	11.48(± 1.83)
	Total	7.87(±2.88)	33.69(±8.61)	59.66(±15.34)
TYB-3215(5mg)	IS	2.28(±1.02)	20.85(±3.31)	55.13 ±(8.73)
	5-ISMN(Conjugate)	2.30(±0.18)	7.08(±0.32)	15.94(±1.68)
	2-ISMN(Conjugate)	0.12(±0.03)	0.38(±0.06)	0.49(±0.09)
	5-ISMN(Free)	0.34(±0.05)	1.43(±0.18)	3.02(±0.20)
	2-ISMN(Free)	0.03(±0.01)	0.06(±0.01)	0.10(±0.01)
	ISDN×10³	10.08(±1.71)	12.28(±2.08)	12.28(±2.08)
	Total	5.08(±1.09)	29.81(±3.48)	74.69(±9.12)
TYB-3215(10 mg)	IS	4.32(±2.78)	21.79(±7.33)	44.88(±12.90)
	5-ISMN(Conjugate)	2.06(±0.42)	9.57(±1.00)	17.05(± 1.35)
	2-ISMN(Conjugate)	0.13(±0.03)	0.41(±0.05)	0.51(± 0.06)
	5-ISMN(Free)	0.26(±0.05)	1.54(±0.22)	2.82(± 0.33)
	2-ISMN(Free)	0.03(±0.01)	0.09(±0.01)	0.11(± 0.02)
	ISDN×10³	6.80(±1.60)	9.23(±1.66)	9.23(± 1.66)
	Total	6.81(±2.79)	33.41(±7.96)	65.38(±13.21)
Sustained-release tab. (ISDN 20mg)	IS	2.94(±0.97)	16.23(±2.54)	48.83(± 6.10)
	5-ISMN(Conjugate)	2.30(±0.33)	6.11(±0.47)	11.64(±1.02)
	2-ISMN(Conjugate)	0.12(±0.01)	0.27(±0.03)	0.33(±0.04)
	5-ISMN(Free)	0.34(±0.11)	0.92(±0.14)	1.96(±0.23)
	2-ISMN(Free)	0.02(±0.01)	0.04(±0.01)	0.07(±0.01)
	ISDN×10³	1.71(±0.38)	2.32(±0.42)	2.48(±0.49)
	Total	5.72(±0.85)	23.57(±2.59)	62.83(± 6.50)

[1] mean (±Standard Error) of 8 subjects

observation of an extremely low amount of the unchanged ISDN excreted in the urine indicated that ISDN is extensively metabolized in the body, especially following oral administration, and excreted in the urine mostly as the metabolites. The data in Table 4 indicate that there is no great difference in the fractions of various metabolites excreted among the 3 dosage strengths of TYB-3215. There is also no

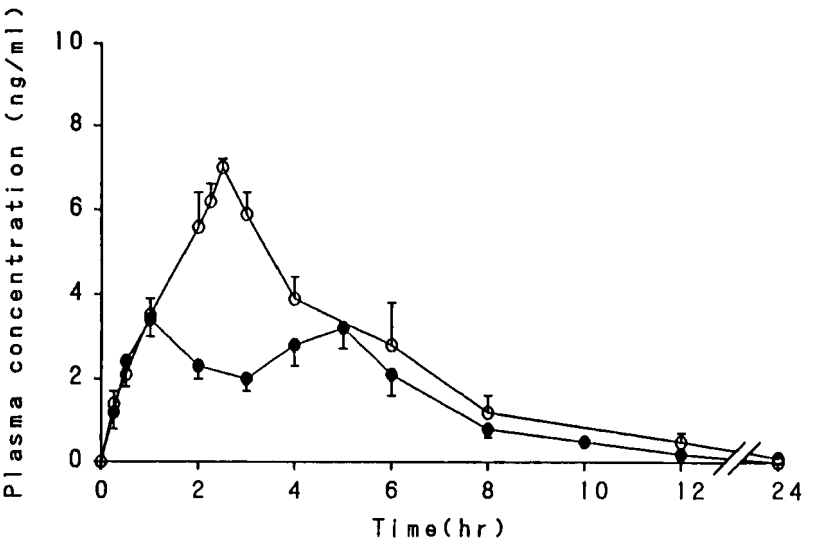


FIGURE 22
Comparative plasma concentration (mean±S.E.) profiles of ISDN following oral administration of TYB-3215 (10mg) in healthy male volunteers (n=5)
Keys : (●) tablet was administrated orally at time zero
(○) tablet was applied to oral mucosa for two hours and then the remainder was swallowed orally

statistically significant difference in the total amounts of excretion between the transmucosal and oral pharmaceutical preparations investigated, since the ISDN absorbed into the body by transmucosal delivery, after bypassing the hepatic "first-pass" metabolism, could be viewed as going through exactly the same pathways of metabolism and excretion as that following oral administration. Furthermore, the fact that the total amount of urinary excretion following the oral mucosa absorption of ISDN from TYB-3215 stays very much at the constant amount of 60 - 75% irrespective to the

administered dose, demonstrating that the urinary excretion of the unchanged compound and its metabolites is almost quantitatively and independent of the dose in the dosage range studied.

2. Pharmacokinetics of ISDN After Oral Administration of TmTs

The plasma concentration profile of ISDN by the oral administration of TYB-3215 (10 mg)to healthy male volunteers is shown in Figure 22[26]. Also shown for comparison is the plasma profile of ISDN from the same TYB-3215 formulation taken orally after a 2-hr gingival application. The results indicate that following the oral administration of TYB-3215, the plasma concentration of ISDN exhibits a bimodal time course with the peak level attained at 1 hr and sustained for another 4 hr, whereas the plasma concentration of ISDN was maintained at constant level of 2 - 3.5 ng/ml. On the other hand, the application of TYB-3215 on gingiva for 2 hrs and then oral administration has yielded a higher plasma concentration (7 ng/ml) of ISDN at around 2.5 hrs after administration. This comparative study suggests that after the 2-hr gingival application, the swallow of TmTs has only resulted in a gradual increase in the plasma level of ISDN, demonstrating that TYB-3215 possesses a sustained releasing character even

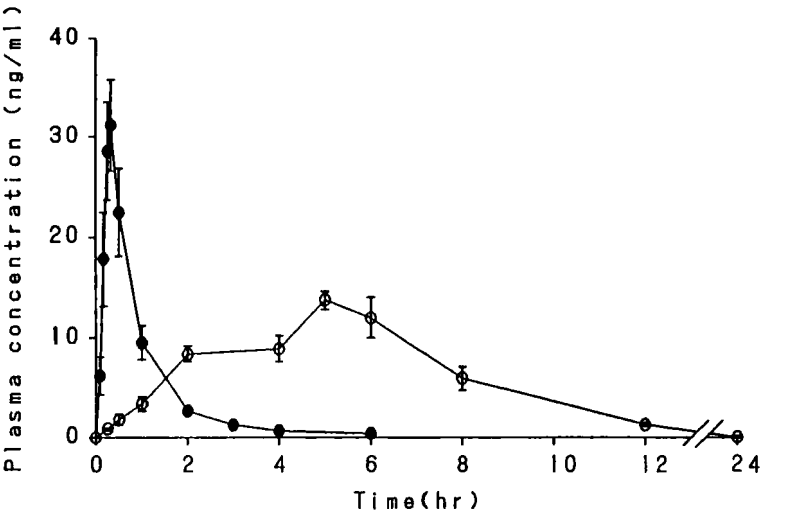


FIGURE 23
Comparative plasma concentration (mean±S.E.) profiles of ISDN : (○) oral mucosa absorption from TYB-3215 (15mg) and (●) sublingual absorption from Nitrol® (5mg) tablet in healthy male volunteers
(TYB-3215, n=5 ; Nitrol®, n=4)

after being swallowed down. No rapid disintegration of its sustained-release layer occurs in the gastrointestinal tract. However, it should be pointed out that TYB-3215 is not so easy to be detached from the gingiva site after the application.

3. Bioavailability and Pharmacokinetics of ISDN Following Oral Mucosa Absorption of TmTs vs Sublingual Tablet

The plasma concentration profiles of ISDN following the gingival application of TYB-3215 (15 mg) and sublingual administration of one conventional

TABLE 5
Pharmacokinetic parameters of ISDN after sublingual absorption from Nitrol® tablet and oral mucosa delivery from TYB-3215 in healthy male volunteers[1]

	pharmacokinetic parameters(mean±SE)				Relative bio-
	Cmax (ng/ml)	Tmax (hr)	MRT (hr)	AUC (ng/ml·hr)	availability(%)
TYB-3215	14.9(±1.4)	5.2(±0.2)	6.0(±0.3)	89.7(±2.5)	111.7(±18.1)
Nitrol® sublingual tablet	32.2(±4.6)	0.3(±0.0)	1.2(±0.1)	28.9(±4.4)	100.0

(1) n=5 (TYB-3215) and n=4 (Nitrol®)

tablet (Nitrol®, 5 mg) are compared in healthy male volunteers[27]. Results are shown in Figure 23 with pharmacokinetic parameters obtained listed in Table 5. The plasma profile of ISDN attained by TYB-3215 is substantially prolonged than that by Nitrol®, with Cmax achieved at 5.2 (± 0.2) hr for TYB-3215, which is much longer than the 0.3 hr for Nitrol®. The MRT value after administration of TYB-3215 is 5 times longer than that by Nitrol®, demonstrating the transmucosal controlled systemic delivery of ISDN from TYB-3215. It is encouraging to observe that the relative bioavailability of ISDN delivered by TYB-3215 is statistically no difference from that attained by the sublingual administration, suggesting that transmucosal systemic delivery is capable of bypassing the hepatic "first-pass" metabolism as does the sublingual absorption.

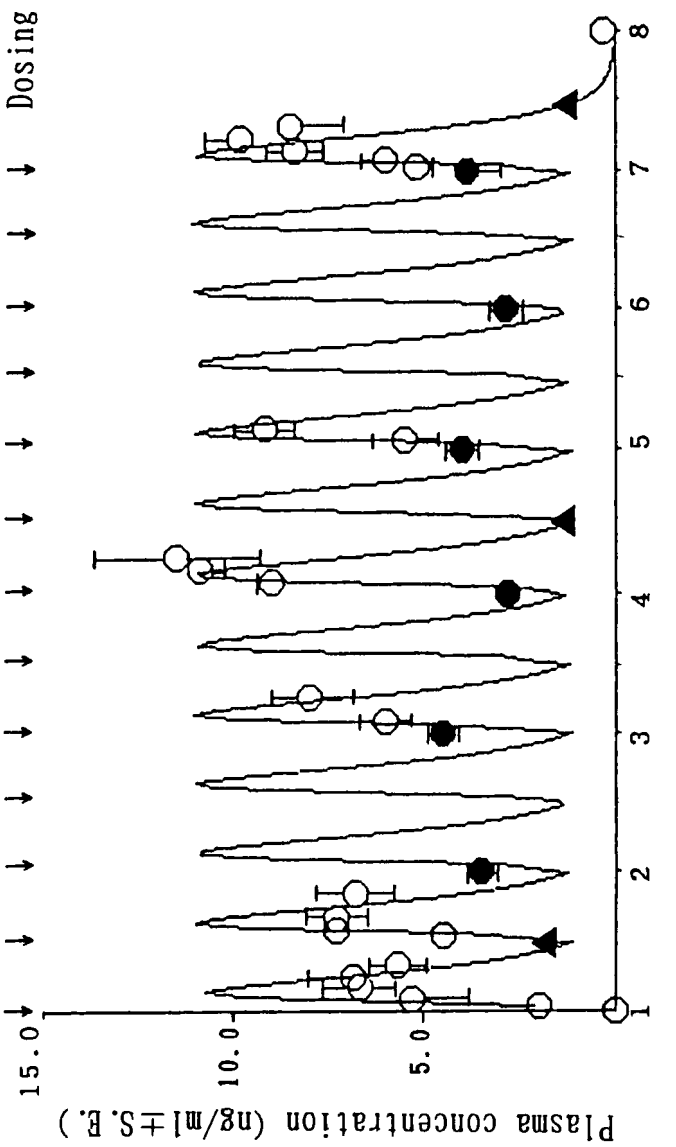


FIGURE 24
Plasma concentration (mean±S.E.) profiles of ISDN following the repeated twice daily gingival application of TYB-3215 at 12 hr interval for 7 days in healthy male volunteers (n=6)
Keys :▲, ●, ○ : actual assay data, —— : simulated curve
▲ : just before application at 9 p.m.
● : just before application at 9 a.m.

4. Pharmacokinetics after Repeated Transmucosal Drug Delivery

The time course for the plasma concentrations of ISDN following the repeated gingival application of TYB-3215 (10 mg) to 6 healthy male volunteers twice daily (9:00 a.m. and 9:00 p.m.) for 7 days (once on Day 7) is shown in Figure 24[28]. Also shown is the simulation curve generated from the pharmacokinetic parameters determined from the single administration (Table 1). It is interesting to note that the concentrations of ISDN actually found coincide rather well with the simulation curve. The results in Figure 24 indicate that steady-state plasma profile of ISDN can be achieved and maintained by twice-a-day gingival application of TYB-3215, which has mean, minimum and maximal plasma concentrations of 5.3, 0.9 and 11.3 ng/ml, respectively. The maximal plasma concentrations of ISDN attained after every administration do not show any tendency of increase, suggesting that no accumulation of ISDN in the body has been resulted from the repeated transmucosal systemic delivery. After the final administration, plasma level of ISDN was observed to be eliminated rapidly from the plasma.

The cumulative urinary excretion profiles of ISDN and its metabolites during the period of repeated administration are shown in Figure 25. The results

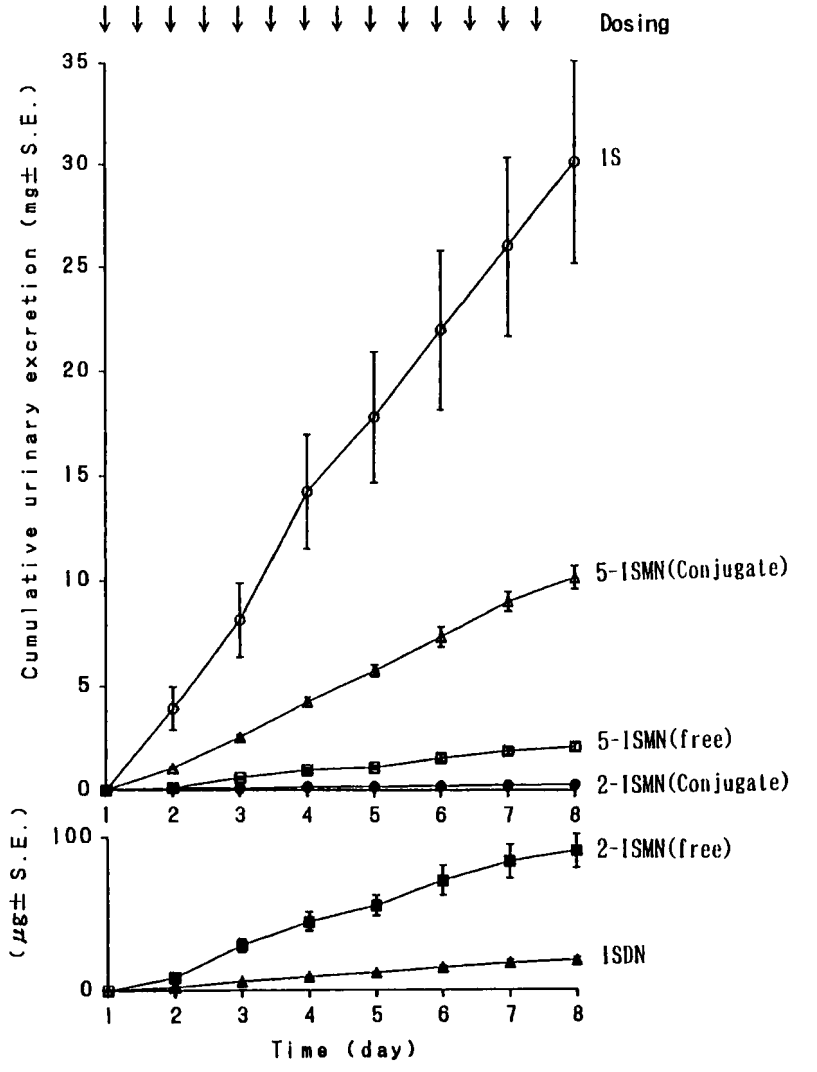


FIGURE 25
Cumulative urinary excretion (mean±S.E.) profiles of ISDN and its metabolites during the 7-day repeated gingival application of TYB-3215 in healthy male volunteers (n=6)

suggest that the excretion of ISDN and its metabolites is relatively constant.

Based on these results, it is concluded that the pharmacokinetics of ISDN after repeated administration of TYB-3215 is linear, and no accumulation has been resulted from the saturation of the absorption or the excretion processes.

PHARMACODYNAMIC STUDIES OF TmTs IN ANGINAL PATIENTS

Short-term Clinical Effecacy

Clinical efficacy of TYB-3215 were first evaluated in 32 patients with stable angina pectoris, after a 2-week baseline pretreatment period. The patients were first administrated with TYB-3215 (5 mg strength) by applying it to the gingival mucosa twice-a-day for 2 weeks, and then the patients were administrated with TYB-3215 (10 mg strength), again twice-a-day, for 2 weeks.

An average of 7.2 anginal episodes/week were recorded in the patients in the baseline pretreatment period, which was decreased to 3.8 episodes/week by TYB-3215 (5 mg) treatment and then to 2.3 episodes/week by TYB-3215 (10 mg) treatment (Figure 26)[29].

The effects on exercise capacity of these two TYB-3215 preparations, containing 5 mg and 10 mg of ISDN,

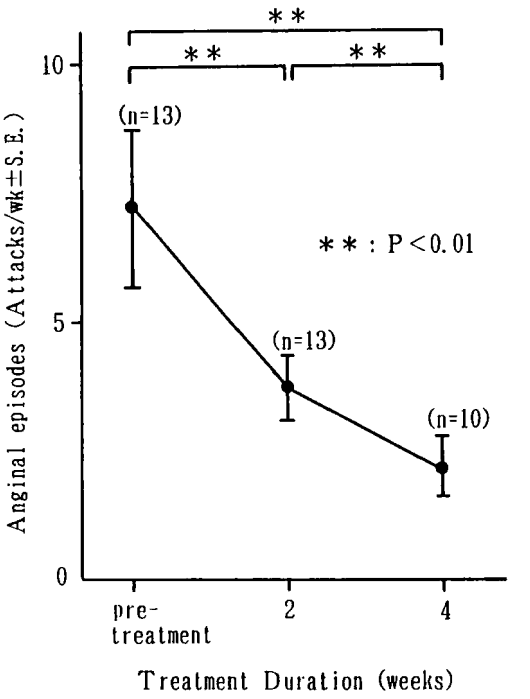


FIGURE 26
Frequency of anginal attacks in the anginal patients (n=32) during the pretreatment and after the treatment with TYB-3215 (5 or 10mg) for two and four weeks

were further assessed in 14 patients with stable exercise-induced angina pectoris. During the one-week pretreatment period, each patient was given a placebo preparation and treadmill exercise test was carried out; and test was performed again after receiving a single dose of one of the two TYB-3215 preparations.

During the treatment period, each patient received a single dose of either placebo, or one of the two

FIGURE 27
Exercise tolerance time measured by treadmill test at 4 and 8 hrs after the gingival application of either placebo or TYB-3215 (5mg or 10mg strength)

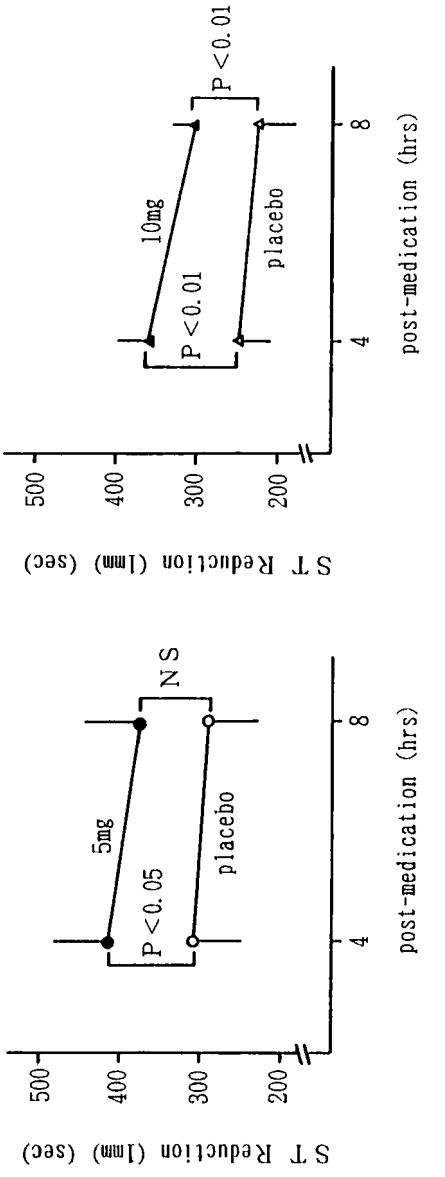


FIGURE 28
Exercise duration to the depression in ST segment (by 1mm) measured at 4 and 8hrs after the gingival application of either placebo or TYB-3215 (5mg or 10mg strength)

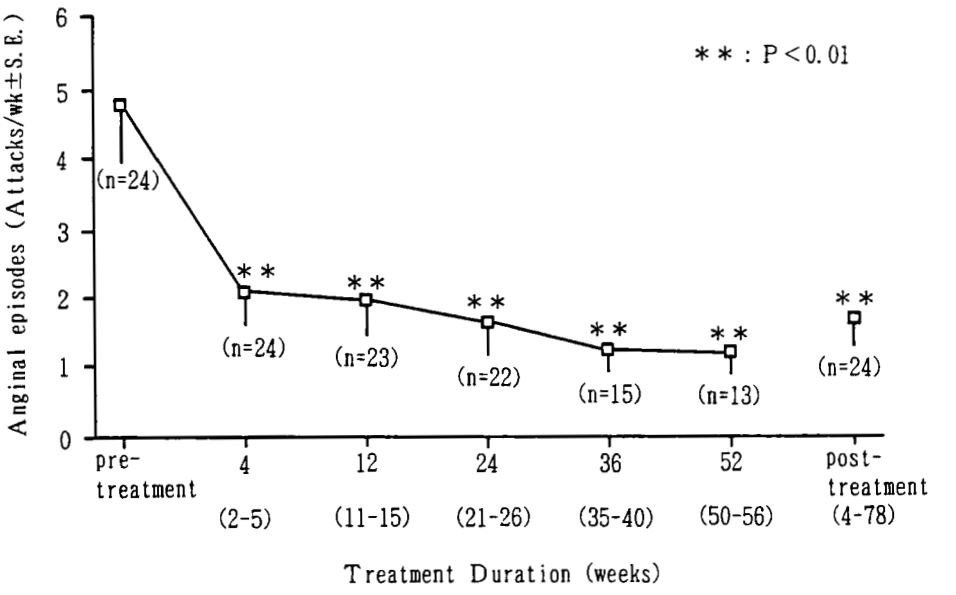


FIGURE 29
Frequency of anginal attacks in the anginal patients (n=25) during the pretreatment and after the treatment with TYB-3215 (5～20mg/day) for up to an duration of 52 weeks

active TYB-3215 preparations. The treadmill exercise tests were then performed 4 and 8 hours after receiving each preparation. The results indicated that in comparison with placebo, both TYB-3215 preparations have induced an increase in the total duration of exercise tolerance and in the exercise duration to the ST segment depression (by 1mm), at both 4 and 8 hours after dosing (Figures 27 and 28)[30].

Long-term clinical Efficacy

TYB-3215 was given twice daily, at 10 mg ~ 20mg/day, to 25 patients with angina pectoris for an average of 46 weeks.

The results demonstrated that the frequency of anginal attacks has been markedly decreased, which shows the attainment and maintenance of a steady anti-anginal effect throughout the treatment period (Figure 29)[31].

CONCLUSION

Since the absorption of drugs through the oral mucosa has been known to be not subjected to the hepatic "first-pass" metabolism, the transmucosal delivery is thus considered an beneficial route of administration for the systemic delivery of drugs which are susceptible to the hepatic "first-pass" metabolism. Thus, anti-anginal drugs, like nitroglycerin (NTG) and isosorbide dinitrate (ISDN) as well as anti-inflammatory enzymes and hormones which are reportedly decomposed in the gastrointestinal tract have been administered clinically in dosage forms, like sublingual or buccal tablets. However, no controlled-(or sustained-) release pharmaceutical preparations have been developed for achieving a prolonged systemic

action via transmucosal controlled delivery. Nitrogard® (Parke-Davis/Warner Lambert., USA), which contains NTG as the active ingredient in a monolayer-type mucoadhesive tablet, is the only preparation commercially available for oral mucosa application to achieve a sustained release of anti-anginal NTG and long-acting systemic medication of angina pectoris for a duration of up to 5 hrs. TYB-3215, a transmucosal therapeutic system which contains ISDN in a bilayered mucoadhesive tablet, has been developed for application to the gingival mucosa with objective of achieving a fast as well as a sustained release of ISDN. It is the first pharmaceutical preparation to consist of a fast- and a sustained-release layers. In this overview, the in vitro release kinetics of ISDN from TYB-3215 was demonstrated. The pharmacokinetics studies in beagle dogs and in human volunteers, the sustained plasma profiles and improved systemic bioavailability of ISDN by transmucosal absorption via the long-term gingival application of TYB-3215 have been demonstrated. With bilayer design, which consists of a fast-release layer and a sustained-release layer, the systemic bioavailability and plasma pharmacokinetic of ISDN have been demonstrated to be superior than those by the conventional sublingual tablet and spray formulations and oral sustained-

release tablet. It is believed that the trans-mucosal therapeutic system described in this paper can be also applied to the transmucosal controlled systemic delivery of therapeutic agents of other therapeutic categories.

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