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Release of Isosorbide Dinitrate from Polymer Film Dosage Forms and Absorption of This Drug through the Oral Mucosa of Rats

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In vitro **release tests and** ***in vivo*** **absorption measurements of oral cavity dosage forms of isosorbide dinitrate (ISDN) prepared from mixed polymer film systems were conducted. Hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose phthalate (HPMCP) were used to make the films, and the tests were conducted with films made from various ratios of these two polymers. The effects of the addition of the accelerator glycyrrhizic acid (GL), on dissolution and absorption were also examined. The mean dissolution time (*** MDT ***) in the** ***in vitro*** **dissolution tests varied with the nature of the polymers and drug, as well as with the pH of the testing solution. The** MDT **for the polymer film system with GL was smaller than that without GL.**

In the ***in vivo*** **absorption tests using rats, the absorption of ISDN through the oral mucosa was observed in all the systems. In the mixed polymer film systems, the mean residence time (** MRT **) increased with increasing the ratio of HPMCP/HPC. The values of the area under the curve (** AUC **) for the systems with GL was larger than for those without GL. A good correlation was demonstrated between the absorption rate constant,** k_a **and the dissolution rate constant,** k_d**.**

Keywords isosorbide dinitrate; glycyrrhizic acid; drug release; drug absorption; oral mucosa

Growing interest is being shown in controlled or sustained drug release through the oral mucosa. This route may be useful for drugs that undergo high first-passage metabolism or are unstable in the gastrointestinal tract. The oral mucosal membrane is readily accessible, and potentially useful as a platform for sustained release devices. However, the oral mucosa has a weak point regarding the absorption and permeation of drugs because of its protective functions. Therefore, an accelerator is indispensable for increasing the permeation and absorption of the drug in order to make it immediately efficient in the blood. Azone and other surfactants have been used as accelerators,[3-6)] but they caused complications and inflammation in the region of administration. Therefore, not only the effect of the acclerator, but also the safety of the administered region must be considered.

In this study, we chose isosorbide dinitrate (ISDN) as a model drug which easily undergoes a first-passage effect at the liver, and we made mixed polymer films with glycyrrhizic acid (GL) as an accelerator and administered the mixture to the oral mucosa. We examined the effect of GL, a substance that accelerates dissolution, on the release of ISDN from mixed polymer films and on the absorption of ISDN through the oral mucosa.

Materials and Methods

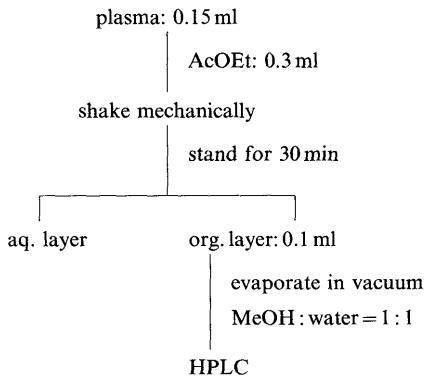
Materials ISDN (Sanyo Yakuhin Kogyo Co., Ltd.) was used as a model drug. The polymers used were hydroxypropylcellulose (HPC, $M_w = 6.0 \times 10^4$), and hydroxypropylmethylcellulose phthalate (HPMCP, $M_w = 4.5 \times 10^4$; both from Shin Etsu Kagaku Kogyo Co., Ltd.). The accelerator used was GL ($M_w = 822.9$, Maruzen Seiyaku).

Preparation of Films One hundred milligrams of ISDN and 5, 10, 15 mg of GL were dissolved in 10 ml of a mixed polymer solution containing 5% HPC and HPMCP, which had been dissolved in acetone. The polymer solution containing ISDN was molded in a Teflon dish (10 cm in diameter, 0.2 cm deep). The solutions were dried at room temperature and kept in a desiccator.

Partition Coefficient Measurement Known amounts of ISDN were equilibrated with equal volumes of octanol and water at 20 °C. The partition coefficient was calculated as the ratio of the amount of drug in each of the two phases.

Dissolution and Release Experiment (a) Dissolution tests for the polymer films were carried out with a JP XII dissolution test apparatus which used a paddle method that bonded one square centimeter of cut square film with double adhesion tape to the inside of a glass vessel with 500 ml of medium at 37±0.1 °C. A paddle rotating speed of 100 rpm was used as the dissolution medium was prepared with a buffered Clark–Lubs solution, and the dissolved polymer films were determined by the weight of the surviving film after it had been dried for a fixed time. This procedure was repeated three times. (b) ISDN release was tested by a JP XII dissolution apparatus-2, which used a paddle method that bonded 1.0 cm^2 of film to the inside of a glass vessel at 37±0.1 °C. The release medium was a buffered Clark–Lubs solution, and the drug concentration was detected by a high performance liquid chromatograph (HPLC, Jasco, Twincle).

Absorption Experiment (a) Animals: Male rats, 8 weeks of age, each weighing 200—210 g, supplied by Clea Japan Inc., Japan were used. (b) The rat, held on a holding plate, was anesthetized with ether. The polymer film dosage was administered on the oral mucosa of the rats, and 0.5 ml of blood was collected from the jugular vein at a fixed time. On the other hand, 1 ml of ISDN (Nitrol injection, Eisai) was injected into the vein to obtain the absolute efficiency of absorption. The ISDN concentration was analyzed by the following method: 30 min after the extraction of blood, blood plasma separated from blood by centrifugation at 3000 rpm, and ISDN, was assayed by HPLC (Jasco, Twincle) as shown in the following scheme:



X-Ray Diffraction Analysis An RAD-IIVC (Rigaku Denki Co., Ltd.) X-ray powder diffraction analyzer was used. The X-ray souce was CuK_α with an Ni filter, at 40 kV, 20 mA, and a scanning speed of 2°/min.

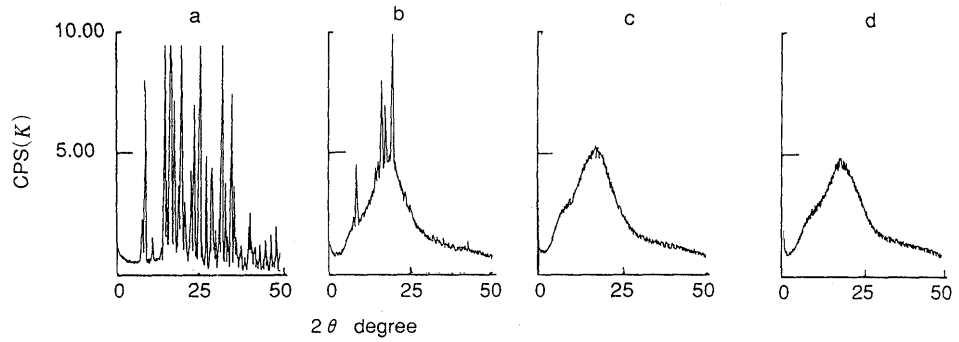


Fig. 1. X-Ray Diffraction Patterns of ISDN and ISDN-Mixed Polymer Films

a, crystalline ISDN; b, ISDN-mixed polymer film without GL; c, ISDN-mixed polymer film with GL; d, mixed polymer film alone.

Results and Discussion

Changes in the Powder X-Ray Diffraction Patterns Figure 1 shows the powder X-ray diffraction patterns of the ISDN in a mixed polymer film with or without GL. Figure 1a shows the diffraction pattern of crystalline ISDN, in which many peaks were observed, but the mixed polymer film of ISDN with GL was found to be amorphous (Fig. 1c). This means that there was no crystalline ISDN in the solid dispersion containing GL.

Effect of GL on the Dissolution of Mixed Polymer Films and ISDN Release from Polymer Film The dissolution rate (K) of mixed polymer films without drug was determined by the weight of the surviving film after it had been dried for the fixed time. Figure 2 shows the effect of GL on the dissolution rate, K, of the polymer films at various pH values. Dissolution was faster when GL was present. This is probably because GL acts as a surfactant and accelerates the wetting between the polymer and the buffered solution.

Figure 3a shows the release of ISDN from various mixed polymer film systems at pH 1. Without GL, ISDN was released more slowly at higher HPMCP/HPC ratios. With GL, ISDN was released slightly faster than when there was no GL. ISDN was released more slowly at higher HPMCP/HPC ratios, probably because HPMCP does not dissolve if the pH of the solution is less than 5.[7] At pH 5, the release profile without GL showed the same tendency as that at pH 1, as shown in Fig. 3b, but with GL, ISDN was released much more quickly than at pH 1, as reported previously.[8] Moreover, the HPC/HPMCP ratio did not affect the ISDN release. In contrast, the rate of ISDN release at pH 7 (Fig. 3c) was the same as that at lower pHs, because HPMCP dissolves in solutions at pH 7.

The mean dissolution time (MDT) was calculated by moment analysis.[9] The mean *in vitro* dissolution time is

$$MDT_{in\ vitro} = \int_0^\infty t(dm/dt) \Big/ \int_0^\infty (dm/dt)dt \quad (1)$$

or

$$MDT_{in\ vitro} = \int_0^\infty t\, dm/m_\infty \quad (2)$$

where m is the amount, concentration, or fraction of drug dissolved in solution at time t, dm/dt is the dissolution rate, and m_∞ is the total amount of drug dissolved in solution, or the final concentration at infinite time.

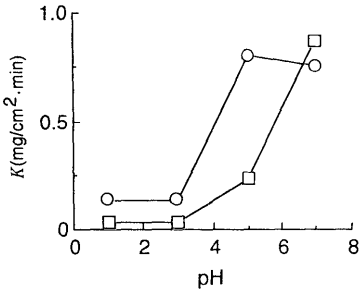


Fig. 2. Relationship between Dissolution Rate Constants (K) of Mixed Polymer Films and pH

○, with GL; □, without GL.

Table I shows that at pH 5, the values of $MDT_{in\ vitro}$ were lower when GL was present, and the dissolution of ISDN was good when 8 mg/cm^2 of GL was added to the pH 5 solution. At pH 7, MDT was independent of the presence of GL. Moreover, MDT could not be calculated from the data of pH 1 solutions, except when the HPC/HPMCP ratio was 2/1, because less than 50% of ISDN was released.[9,10]

Solid dispersions of drugs are made with polymers, which markedly enhance a drug's dissolution rate[11-13] or its sustained release.[14-16] Here, the solid dispersions of ISDN with polymer with the addition of GL result in the transformation of the drug into a GL amorphous form, as shown in Fig. 1. The amorphous form of ISDN might promote the drug release from the mixed polymer films.

Effect of GL on the Absorption Kinetics of ISDN in the Oral Mucosa of Rat The permeability of drugs *via* the oral mucosa is related to the diffusion process of the drugs and is affected significantly by the hydrophobic properties of the drugs.[17] Figure 4 shows the relationship between the logarithm of the partition coefficient (log P octanol/water) and pH for ISDN. The values of log P were large at all pH values and did not change with the pH values. These findings indicated that ISDN is easily absorbed *via* the oral mucosa owing to poor dissociation.

Figure 5 shows the plasma concentrations of ISDN when ISDN was administered on the oral mucosa of rats. The maximum plasma concentration of ISDN decreased with increasing HPMCP/HPC ratio in the mixed polymer films, both in the presence and absence of GL. Moreover, the highest level of ISDN was absorbed when GL was

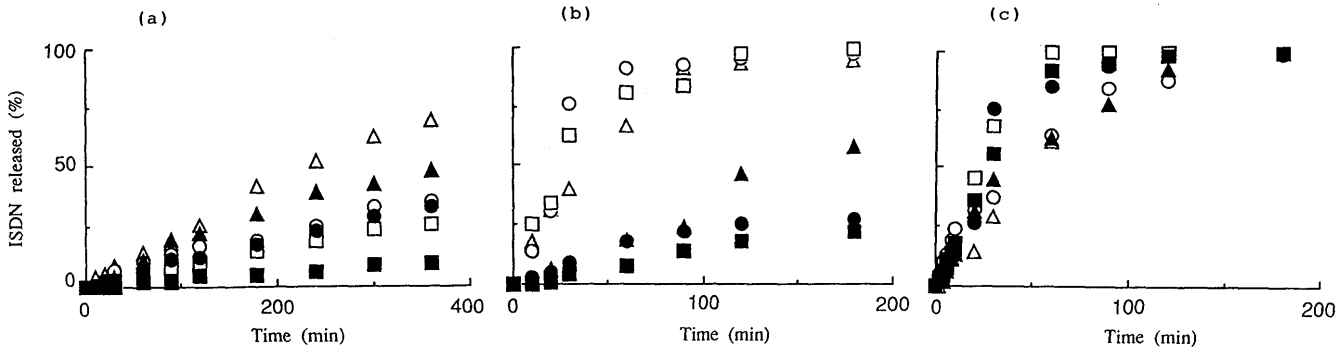


Fig. 3. Release Profiles of ISDN from Mixed Polymer Films

(a) pH 1.0; (b) pH 5.0; (c) pH 7.0. △, HPC/HPMCP=2/1 with GL (8 mg/cm²); ○, HPC/HPMCP=1/1 with GL (8 mg/cm²); □, HPC/HPMCP=1/2 with GL (8 mg/cm²); ▲, HPC/HPMCP=2/1 without GL; ●, HPC/HPMCP=1/1 without GL; ■, HPC/HPMCP=1/2 without GL.

TABLE I. The Mean *In Vitro* Dissolution Time (*MDT*) of ISDN from Mixed Polymer Film

Sample		HPC/HPMCP=2/1		
GL (mg/cm²)	0	4	8	12
pH 1.0	2.74	2.46	2.46	2.40
pH 5.0	2.46	1.21	0.71	0.91
pH 7.0	0.76	0.81	0.88	0.86
Sample		HPC/HPMCP=1/1		
pH 1.0	—	—	—	—
pH 5.0	—	0.92	0.49	0.96
pH 7.0	0.88	0.79	0.53	0.94
Sample		HPC/HPMCP=1/2		
pH 1.0	—	—	—	—
pH 5.0	—	0.94	0.64	0.81
pH 7.0	0.49	0.79	0.55	0.70

—: impossible to calculate *MDT*, since ISDN released was less than 50%.

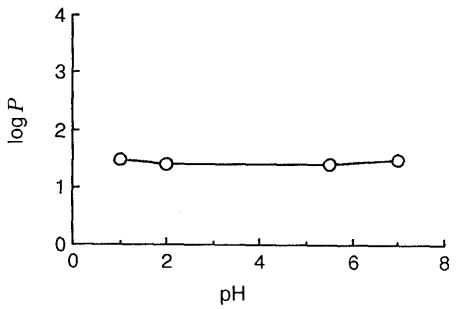


Fig. 4. Relationship between Logarithm of Partition Coefficient (log *P*) and pH

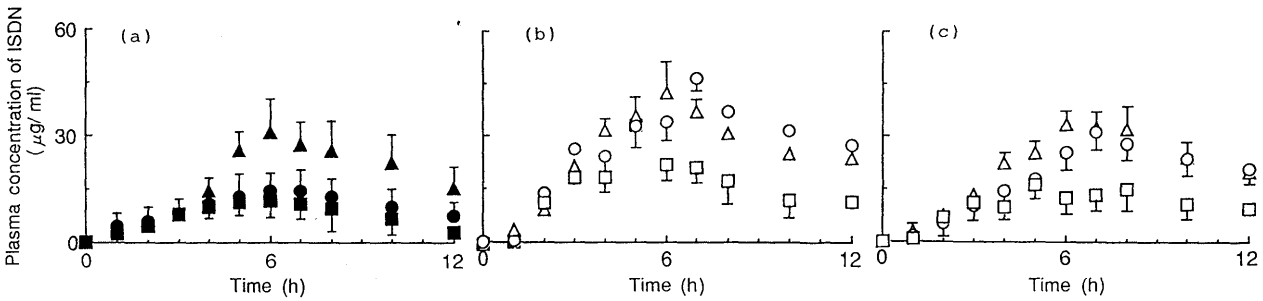


Fig. 5. Plasma Concentrations of ISDN after Administration on the Oral Mucosa of Rats ($n=6$)

(a) Without GL; (b) with GL of 8 mg/cm²; (c) with GL of 12 mg/cm². ▲, △, HPC/HPMCP=2/1; ●, ○, HPC/HPMCP=1/1; ■, □, HPC/HPMCP=1/2.

added at 8 mg/cm². Therefore, the optimum concentration of GL in the polymer film is 8 mg/cm².

The effect of GL on the absorption of ISDN *via* the oral mucosa was examined. The moment analysis method was used to calculate the area under the curve (*AUC*), extent of bioavailability (*F*), mean residence time (*MRT*), mean absorption time (*MAT*), and absorption rate constant (k_a), as listed in Table II.

The values of the *AUC* were increased with an increasing concentration of GL, and the highest value was obtained by the addition of 8 mg/cm² of GL. The values of both *F* and k_a showed the same tendency as the *AUC*. These findings suggest that the bioavailability of ISDN is improved by the addition of GL, and that the optimum concentration of GL is 8 mg/cm². On the other hand, the values of *MRT* changed only slightly with the addition of GL when the ratio of HPMCP/HPC was 1/2. However, in the other mixed films with different HPMCP/HPC ratios, the values of *MRT* increased with increasing GL concentration. The values of *MAT* showed almost the same tendency as *MRT*. These findings suggest that GL improves the absorption of ISDN efficiently through the oral mucosa of the rat. These plasma concentration data were simultaneously fitted to a two-compartment model with a first-order absorption process, as shown in Fig. 6, using an automated pharmacokinetic analysis system, APAS.[18]

Figure 7 shows the plasma concentration–time profiles for ISDN comparing the data at the HPC/HPMCP ratio of 1/1. The absorption of ISDN from the oral mucosa in

TABLE II. Bioavailability of ISDN in Mixed Polymer Film Systems

Sample		HPC/HPMCP=2/1		
GL (mg/cm²)	0	—	8	12
AUC (μg·h/ml)	315.7±80.0		509.1±40.4	350.4±81.2
MRT (h)	10.9± 2.04		10.4± 2.53	10.2± 1.80
MAT (h)	10.6		10.1	9.86
F (—)	0.24		0.39	0.27
k_a (h^{-1})	0.55		0.61	0.44
Sample		HPC/HPMCP=1/1		
GL (mg/cm²)	0	—	8	12
AUC (μg·h/ml)	171.1±78.9	328.4±69.1	563.5±60.9	433.1±133.1
MRT (h)	9.9± 2.9	11.3± 2.3	13.6± 1.9	15.3± 1.9
MAT (h)	9.64	11.1	13.3	15.1
F (—)	0.13	0.25	0.43	0.33
k_a (h^{-1})	0.43	0.40	0.60	0.41
Sample		HPC/HPMCP=1/2		
GL (mg/cm²)	0	—	8	12
AUC (μg·h/ml)	100.1±29.2		270.8±50.2	216.9±65.9
MRT (h)	7.7± 0.5		12.8± 4.3	13.5± 5.4
MAT (h)	7.12		12.5	13.2
F (—)	0.08		0.21	0.17
k_a (h^{-1})	0.36		0.60	0.49

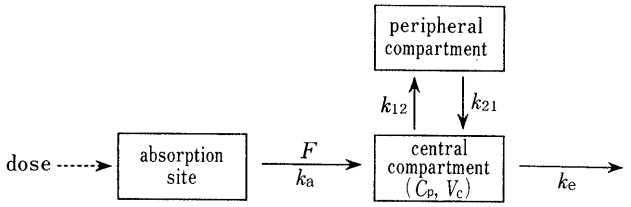


Fig. 6. Illustration of Two-Compartment Model with First-Order Absorption

k_{12}, k_{21}, first-order distribution rate constants; k_e, first-order elimination rate constant; V_c, first-order central compartment; k_a, first order absorption rate constant; F, fraction of dosage absorbed.

the rat was fitted to a two-compartment model by the APAS, but the absorption rate constant, k_a, was the only parameter of pharmaceutical kinetics compared, because the F values were very small.

The release of ISDN was almost zero-order and it is easily absorbed after being dissolved from the film dosage forms due to its non-dissociation property, but the mechanism involves very complicated processes. The relationship among $MDT_{in\ vitro}$, $MDT_{in\ vivo}$, snd k_d which is obtained from the linear relationship among the percent of ISDN released, time of release and k_a, were analyzed using *in vitro* and *in vivo* data. $MDT_{in\ vivo}$ was calculated by the following equation:

$$MDT_{in\ vivo} = MRT_{film} - M_{solution} \quad (3)$$

Figure 8 shows the relationship between k_d and k_a at pH 5. These results demonstrated a good linear relationship for ISDN.

Conclusions

The film dosage forms of ISDN showed sustained release by changing the HPC to HPMCP ratio in the polymer, and the dissolution of this drug was increased by the addition of GL. Moreover, the absorption of ISDN *via* oral mucosa in the rat was also increased by the addition of GL.

For the film dosage forms of ISDN, a good correlation was demonstrated between k_d and k_a which was calculated by moment analysis.

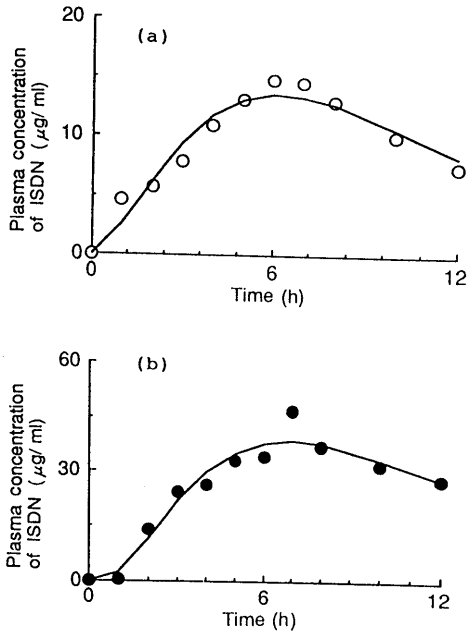


Fig. 7. ISDN Concentrations in Plasma Fitted by the Two Compartment Model Analysis, for HPC/HPMCP=1/1

(a) Without GL; (b) with GL of 8 mg/cm². ○, ●, observed; —, calculated.

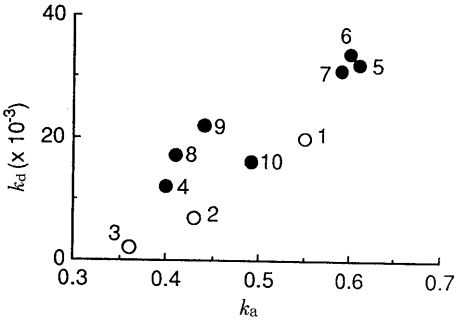


Fig. 8. Relationship between k_a and k_d of ISDN (r=0.830)

○, without; ●, with. 1, HPC/HPMCP=2/1 without GL; 2, HPC/HPMCP=1/1 without GL; 3, HPC/HPMCP=1/2 without GL; 4, HPC/HPMCP=1/1 with GL of 4 mg/cm²; 5, HPC/HPMCP=2/1 with GL of 8 mg/cm²; 6, HPC/HPMCP=1/1 with GL of 8 mg/cm²; 7, HPC/HPMCP=1/2 with GL of 8 mg/cm²; 8, HPC/HPMCP=2/1 with GL of 12 mg/cm²; 9, HPC/HPMCP=1/1 with GL of 12 mg/cm²; 10, HPC/HPMCP=1/2 with GL of 12 mg/cm².

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