Preparation and Evaluation of Eudragit Gels. V. Rectal Gel Preparations for Sustained Release and Avoidance of First-Pass Metabolism of Lidocaine

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The release of lidocaine from hydrogel and xerogel preparations was remarkably suppressed compared with polyethylene glycol (PEG) 2000 suppository. The release rate of lidocaine from hydrogel and xerogel increased with the increase in the amount of sodium hydroxide incorporated within the range of 3 to 7 milliequivalent (meq). After an oral administration of lidocaine HCl solution, the plasma concentration of lidocaine was considerably lower than that after intravenous administration for all time periods. The absolute bioavailability (F_{oral}) was 5.63%. For the Witepsol S-55 and PEG 2000 suppositories, the plasma levels of lidocaine were higher than those for the oral preparation, and C_{max} and area under the concentration–time curve (AUC) values significantly improved ($p<0.01$). The absolute bioavailabilities were 21.3 and 29.6%, respectively. On the other hand, Eudispert hv-hydrogel and xerogel preparations showed the characteristics of a sustained-release preparation, especially the xerogel preparation with 5 meq NaOH. Absolute bioavailability for hydrogel and xerogel preparations increased significantly ($p<0.05$) by approximately 1.7—3.4 folds compared with those of Witepsol S-55 and PEG 2000 suppositories.

Keywords Eudispert hv-rectal gel; lidocaine; first-pass metabolism; bioavailability; sustained release; suppository; hydrogel; xerogel; swelling; rabbit

Lidocaine is widely used by the intravenous route for the treatment of ventricular arrhythmias, particularly when associated with acute myocardial infarction.[1,2] However, its use is restricted by the need for parenteral administration. The short elimination half-life of lidocaine, approximately 1.5 h in man, means that an i.v. infusion is required to keep the plasma concentration within the therapeutic range when the drug is given for longer than a few hours.[3-7] Since there is a well-established relationship between drug concentration and antiarrhythmic activity, attempts have been made to utilize routes other than the intravenous route to achieve desired blood levels.[7-10] Bioavailability of lidocaine given *p.o.* is low because of extensive first-pass metabolism in the liver, but the large doses needed cause high concentrations of toxic metabolites.[5-7] Boer *et al.* and many investigators have reported that the bioavailability of lidocaine after rectal administration is substantially higher than that after oral administration.[11-16]

In the previous papers,[17-22] we reported on the preparation and potential use of new gel bases as a suppository using Eudragit L, S, and Eudispert, which are block copolymers of methacrylic acid and methyl methacrylate. These hydrogel and xerogel preparations showed excellent localization and bioadhesive effects in the lower part of the rectum in rats[19] and rabbits.[20] The hepatic first-pass elimination could be avoided to a maximal degree when Eudispert hv-hydrogel and xerogel preparations containing a drug such as pentoxifylline,[19] propentofylline,[20] or salicylamide[21] were administered.

This study was designed to show whether a new rectal gel preparation containing lidocaine hydrochloride (HCl) given per rectum would reduce hepatic metabolism and sustain plasma concentrations of the drug in rabbits.

Experimental

Materials Eudispert hv was a gift from the Higuchi Co. (Tokyo, Japan). Witepsol S-55 was the product of Maruishi Pharmaceutical Co. (Osaka, Japan). Polyethylene glycol (PEG) 2000 was the product of Nakalai Tesque Co. (Kyoto, Japan). Lidocaine HCl was prepared from lidocaine base (Sigma Chemical Co., St. Louis, MO, U.S.A.) as follows: lidocaine base (10 g) was dissolved in ethyl ether (500 ml). After passing through fresh sulfuric acid for purification, HCl gas was introduced into the above ethyl ether solution. A precipitate (lidocaine HCl) was formed in ethyl ether, filtrated and washed three times with 500 ml of each fresh ethyl ether and then dried in a vacuum drying oven at 40 °C for 48 h. All other reagents and solvents were of analytical grade.

Preparation of Eudispert hv Rectal Gels and Other Suppositories Lidocaine HCl 2.5 g was dissolved in 52.5 to 87.5 g of purified water, and then Eudispert hv was added to 10% (w/w) to the total weight. The mixture was mechanically stirred with a propeller (MDC Stirrer 2S type, Tokyo Rikakikai Co., Tokyo, Japan) at 200 rpm and allowed to soak and swell for 10 min. Then, 8% (w/w) NaOH solution (3 to 7 meq) was added to the resulting mixture while stirring. Hydrogel preparations (2.0 g) containing 2.5% (w/w) lidocaine HCl were obtained by the procedure described above. Xerogel preparations were obtained by the freeze-drying method reported previously.[20] The other suppositories were prepared by a fusion method. In brief, lidocaine HCl was dissolved in each suppository base at 45—60 °C by mechanical stirring with a propeller at 200 rpm at a concentration of 2.5% (w/w). The mixture was cooled gradually in specially made plastic molds[20] for rectal administration to rabbits. The completed suppository (2 g) was a cylindrical shape with a 9 mm diameter base and a hight of 30 mm.

Measurement of pH of the Hydrogels The pH of 5% (w/w) Eudispert hv-hydrogels, with 3, 5, 7, 7.5, or 8 meq of sodium hydroxide, containing 2.5% lidocaine or 2.5% lidocaine HCl was measured with a pH meter (Horiba L-7LC, Horiba Ltd., Kyoto, Japan) and compared with that of hydrogels containing no drug.

Swelling Properties of Hydrogels, Xerogels and Suppositories The apparatus and method were basically the same as the rotating basket method stipulated in the JP XI except that the preparations inserted into a cellulose tube (Viskase Sales Corp., flat width 32 mm, diameter 20 mm). After 2.0 g of hydrogels, xerogels (equivalent to hydrogel 2.0 g), PEG 2000 and Witepsol S-55 suppository bases were inserted in a cellulose tube, both ends of the tube were ligated to obtain 50 mm of the length (weight = W_1), and introduced into the basket. Tests were started immediately in deionized water (900 ml) at 37 °C and with a rotation speed of 100 rpm. At appropriate time intervals, the weights of the swelled samples were measured (W_2). Swelling ratios were calculated using the following equations.

$$\text{swelling ratio} = \frac{\text{weight(g) of swelled gel at time } t}{\text{initial weight(g) of gel}} = \frac{2.0 + (W_2 - W_1)}{2.0}$$

***In Vitro* Release Study** The apparatus and method were basically the same as described above. After 2.0 g of hydrogels, xerogels (equivalent to hydrogel 2.0 g), and PEG 2000 suppository, containing 50 mg of lidocaine base or lidocaine HCl in each preparation, were inserted in a cellulose tube, both ends of the tube were ligated to obtain 50 mm of the length. They were introduced into a basket and tests were started immediately. A one-milliliter aliquot sample was taken out at appropriate time intervals

with the medium replaced by 1 ml of the fresh test solution at the same temperature. The sample solution was then introduced into the high-performance liquid chromatography (HPLC) (Model LC-6A, Shimadzu Seisakusho Co., Kyoto, Japan) for the assay of lidocaine. An octadecyl silica column (Shim pack CLS ODS, 0.6 × 15 cm, particle diameter 5 μm, pore diameter 100 Å) was employed, and measurement was made at a wavelength of 205 nm. The mobile phase was made up of methanol–acetonitrile–water (3 : 16.3 : 80.7; v/v). The flow rate and column temperature were 1.5 ml/min and 40 °C, respectively.

HPLC Assay of Lidocaine in Plasma The concentration of lidocaine in plasma was determined by the HPLC method, employed pentoxifylline as the internal standard. To 1.0 ml of plasma, 0.1 ml of pentoxifylline solution (10 μg/ml) and 5 ml of methylene chloride were added. The mixture was shaken for 10 min for extraction. The resulting mixture was centrifuged at 3000 rpm for 10 min, and then 4 ml of the organic layer was collected and evaporated to dryness at 45 °C. To the residue was added 0.2 ml of a mobile phase (methanol : acetonitrile : water = 3 : 16.3 : 80.7) and the mixture was thoroughly mixed. HPLC was performed for measurement of lidocaine under the same conditions described above. In this assay method, the recovery percentages of lidocaine and internal standard (pentoxifylline) from plasma were 101.6 ± 1.14 (S.D.)% (n = 18) and 101.8 ± 2.32 (S.D.) % (n = 18), respectively. The calibration curve of lidocaine was linear in the range of 0.05 to 20 μg/ml, and linear regression analysis of the data gave a correlation coefficient (r) consistently greater than 0.999; the coefficients of variation calculated from the peak area ratio during the experimental period were less than 5%.

Rectal Administration in Rabbits In white male rabbits (JW, Japan SLC Co., Shizuoka, Japan) weighing 3—3.5 kg that had been fasted for 48 h, 10% Eudispert hv-hydrogels with 5 and 7 meq NaOH, Eudispert hv-xerogels with 5 and 7 meq NaOH, PEG 2000, and Witepsol S-55 suppositories containing 50 mg of lidocaine HCl were administered into the rectum of the rabbits 3 to 4 cm above the anus. Then, the anus was closed with a clip to prevent possible leakage. Thereafter, 2.5 ml of blood was collected at suitable time intervals. The collected blood was immediately centrifuged at 8000 rpm for 5 min to obtain plasma. The plasma samples were frozen at −30 °C until analyzed.

Intravenous and Oral Administration to Rabbits A constant-rate intravenous infusion of 1% lidocaine HCl solution (in 5 ml of saline solution) was given through the left marginal ear vein over a period of 30 min using a Micro-feeder (JP-V type, Furue Science Co., Tokyo, Japan). The 0.5% lidocaine HCl solution (in 10 ml of aqueous solution) was orally administered to the rabbits with controlled gastric emptying rates. The gastric emptying rates were controlled according to the method reported previously.[20] sampling of blood and assay of lidocaine were done as described above.

Data Analysis The area under the plasma concentration–time curve (AUC) was calculated according to a trapezoidal rule with an extrapolation to infinity. Absolute bioavailability of lidocaine given orally (F_{oral}) and rectally (F_{rect}) was calculated as reported previously.[20] Statistical analysis was performed using one-way analysis of variance ($p<0.05$, $p<0.01$), followed by Fisher's pairing t test for differences.

Results and Discussion

Swelling Property of Hydrogels, Xerogels and Suppositories Figure 1 shows the time courses of swelling ratios of 10% Eudispert hv-hydrogels, PEG 2000 and Witepsol S-55 suppository bases. The neutralization by NaOH for carboxylic acid in Eudispert changes the swelling property of the hydrogel prepared. As the largest amount of sodium hydroxide was incorporated in hydrogels within the range of 1 to 7 meq, the swelling ratio of Eudispert hydrogels increased gradually. Similar results were obtained in Eudispert hv-xerogels. The swelling rate calculated from a slope of straight line in Fig. 1. were 0.048—0.87 g/h for Eudispert hv-gels and 3.57 g/h for PEG 2000. Accordingly, the swelling property of Eudispert hv-gels is considered at least below 1/4 fold compared with that of PEG 2000.

Effect of Lidocaine or Lidocaine HCl on the pH of Eudispert hv-Hydrogels The results of measurement of pH of 5% Eudispert hv-hydrogels, with 3, 5, 7, 7.5, and 8 meq sodium hydroxide, containing 2.5% lidocaine base, lidocaine HCl, or no drug are summarized in Table I. If the amount of sodium hydroxide incorporated was more the 7.5 meq in hydrogels containing no drug, the hydrogels were strongly alkaline, and not clinically applicable. When 2.5% of lidocaine base (pK_a = 8) was contained in hydrogels with the incorporation range of sodium hydroxide below 7.5 meq, the pH of the hydrogels increased compared with those of the hydrogels containing no drug, whereas the incorporation of lidocaine hydrochloride decreased the pH of the hydrogels.

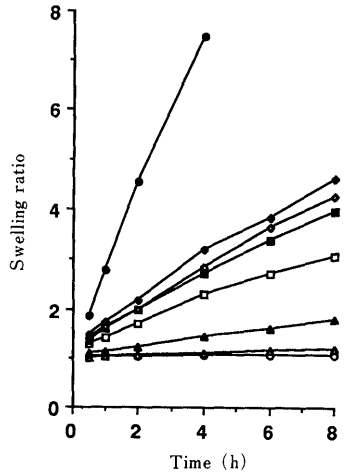

Fig. 1. Time Courses of Swelling Ratio for Witepsol S-55 (○), PEG 2000 (●) and 10% Eudispert hv-Hydrogels with 1 meq (△), 2 meq (▲), 3 meq (□), 4 meq (■), 5 meq (◇) and 7 meq (◆) of Sodium Hydroxide

Each point represents the mean of three experiments.

Table I. Effect of Lidocaine Base or Lidocaine HCl on the pH of 5% Eudispert hv-Hydrogels with Sodium Hydroxide

NaOH added (meq)	pH of 5% Eudispert hv-hydrogels		
	No drug	2.5% Lidocaine	2.5% Lidocaine HCl
3	5.76 ± 0.13	6.35 ± 0.03	5.74 ± 0.06
5	6.21 ± 0.10	7.32 ± 0.03	6.13 ± 0.09
7	7.25 ± 0.15	8.06 ± 0.01	7.11 ± 0.06
7.5	8.32 ± 0.89	8.97 ± 0.02	7.36 ± 0.05
8	10.72 ± 0.78	9.61 ± 0.11	7.49 ± 0.09

Each value represents the mean ± S.D. of three experiments.

Release of Lidocaine from Hydrogels, Xerogels, and PEG 2000 Suppository Containing Lidocaine or Lidocaine HCl Figure 2 shows the release profiles of lidocaine from 10% Eudispert hv-hydrogel and xerogel preparations, with 5 and 7 meq sodium hydroxide, and PEG 2000 suppository, containing 2.5% lidocaine HCl. The release of lidocaine from hydrogel and xerogel preparations was remarkably suppressed compared with PEG 2000 suppository. Also, the releases of lidocaine from xerogel preparations, especially from gel preparations with 5 meq sodium hydroxide, were more suppressed than those from other hydrogel preparations. The profiles in Fig. 3 show the effects of the incorporated amount of sodium hydroxide on the release rate of lidocaine from 10% Eudispert hv-hydrogel and xerogel preparations containing lidocaine base or lidocaine HCl. The release rate of lidocaine from hydrogel and xerogel

increased with the increase in the amount of sodium hydroxide incorporated within the range of 3 to 7 meq. Moreover, the release rate of lidocaine from the gel preparations containing lidocaine HCl was larger than those from the gel preparations containing lidocaine base. However, little difference in the release rate of lidocaine from the gel preparations containing either lidocaine base or lidocaine HCl was shown when a large amount of sodium hydroxide, *e.g.* 7 meq, was incorporated.

Plasma Concentration–Time Curves of Lidocaine after Intravenous, Oral, and Rectal Administration to Rabbits Figure 4 shows the mean plasma concentration–time curves of lidocaine after intravenous infusion, oral, and rectal administration of lidocaine HCl. The bioavailability parameters are summarized in Table II. After intravenous infusion for 30 min, plasma concentration of lidocaine reached a maximum value ($C_{max}=5.5\,\mu g/ml$), and then rapidly declined as shown in Fig. 4A. A biphasic disposition was shown from the plasma concentration profile. The elimination half-lives of lidocaine were 1.58 min for the α-phase and 41.7 min for the β-phase, respectively. After oral administration, the plasma concentration of lidocaine was considerably lower than after the intraveous administration for all time periods. The maximum concentration ($C_{max}=0.18\,\mu g/ml$) was attained at 30 min after oral administration of the lidocaine HCl solution. Lidocaine was then rapidly eliminated from the plasma, with an apparent elimination half-life of 49.1 min. The absolute bioavailability (F_{oral}) was 5.63%.

For the Witepsol S-55 and PEG 2000 suppositories, the plasma levels of lidocaine were higher than that for the oral preparation, and C_{max} and AUC values were improved significantly ($p<0.01$) as shown in Table II. The apparent half-lives were 54.8 and 61.6 min, and absolute bioavailabilities, were 21.3 and 29.6%, respectively. On the other hand, Eudispert hv-hydrogel and xerogel preparations produced obvious features of a sustained-release preparation, especially the xerogel preparation with 5 meq NaOH, as shown in Fig. 4B. The C_{max} for hydrogel and xerogel preparations with 7 meq NaOH increased significantly ($p<0.05$), and the time to reach maximum plasma

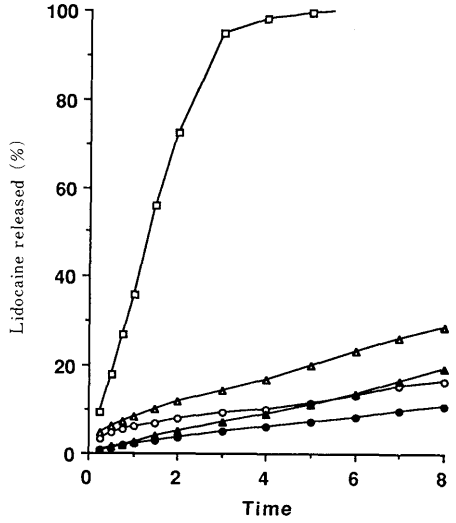

Fig. 2. Release Profiles of Lidocaine from PEG 2000 (□), 10% Eudispert hv-Hydrogel with 5 meq NaOH (○) or 7 meq NaOH (△), and Eudispert hv-Xerogel with 5 meq NaOH (●) or 7 meq NaOH (▲) Containing 50 mg of Lidocaine HCl

Each point represents the mean of three experiments.

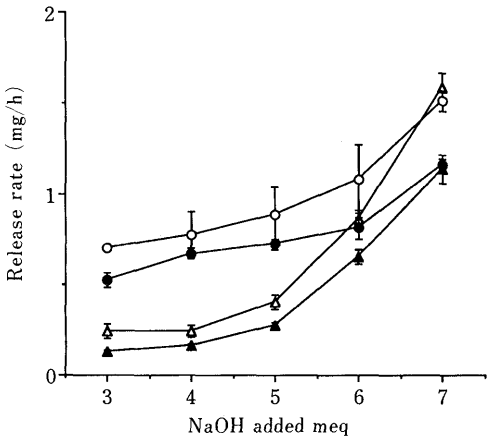

Fig. 3. Effect of Sodium Hydroxide on the Release Rate of Lidocaine from 10% Eudispert hv-Hydrogels Containing Lidocaine Base (△) or Lidocaine HCl (○), and from Eudispert hv-Xerogels Containing 50 mg of Lidocaine Base (▲) or Lidocaine HCl (●)

Each point represents the mean ± S.D. of three experiments.

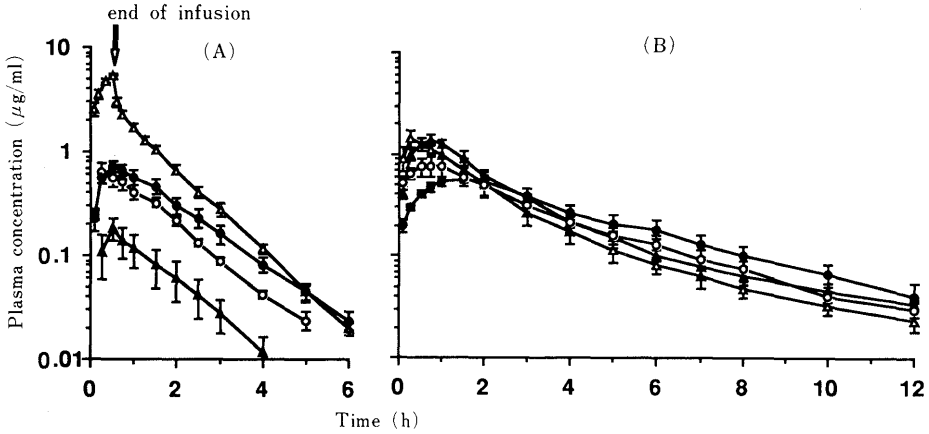

Fig. 4. Time Course of Plasma Concentrations after Intravenous, Oral, and Rectal Administration of Lidocaine HCl to Rabbits with a Dose of 50 mg/body ($n=4$—6; mean ± S.E.M.)

(A) △, intravenous infusion; ▲, oral solution; ○, Witepsol S-55 suppository; ●, PEG 2000 suppository. (B) △, 10% Eudispert hv-hydrogel with 7 meq NaOH; ▲, 10% Eudispert hv-hydrogen with 5 meq NaOH; ○, Eudispert hv-xerogel with 7 meq NaOH; ●, Eudispert hv-xerogel with 5 meq NaOH.

TABLE II. Bioavailability Parameters of Lidocaine after Intravenous, Oral, and Rectal Administrations of Lidocaine HCl at a Dose of 50 mg/body to Rabbits

Administrations (*n*)	C_{max} (μg/ml)	T_{max} (h)	AUC_0^∞ (μg·h/ml)	$F^{a)}$ (%)
i.v. infusion (5)	5.50±0.15	0.50	5.07±0.31	100
Oral solution (4)	0.18±0.05	0.50	0.29±0.10	5.63± 2.01
Witepsol S-55 suppository (6)	0.69±0.14[b)]	0.33±0.05	1.08±0.12[b)]	21.3 ± 2.41
PEG 2000 suppository (6)	0.76±0.08[b)]	0.54±0.08	1.50±0.23[b)]	29.6 ± 4.50
10% Eudispert hv-hydrogel with 5 meq NaOH (5)	0.85±0.17	0.65±0.13	2.77±0.54[c)]	54.7 ±10.7
Eudispert hv-xerogel with 5 meq NaOH (6)	0.61±0.15	1.92±0.24[c,e)]	2.97±0.45[c)]	58.5 ± 8.82
10% Eudispert hv-hydrogel with 7 meq NaOH (6)	1.54±0.24[c,d)]	0.42±0.12	3.19±0.57[c)]	62.9 ±11.3
Eudispert hv-xerogel with 7 meq NaOH (4)	1.40±0.14[c,d)]	0.81±0.06	3.66±0.24[c)]	72.2 ± 4.77

a) $F=[AUC_0^\infty]_{\text{oral or rectal}}/[AUC_0^\infty]_{\text{i.v.}}$. *b)* $p<0.01$ *versus* oral solution. *c)* $p<0.05$ *versus* Witepsol S-55 and PEG 2000. *d)* $p<0.05$ *versus* hydrogel and xerogel preparations with 5 meq NaOH. *e)* $p<0.05$ *versus* hydrogel preparations. Each value represents the mean±S.E.M.

concentration (T_{max}) for xerogel preparations was delayed significantly ($p<0.05$) compared with those for other suppository preparations. Absolute bioavailability for hydrogel and xerogel preparations increased significantly ($p<0.05$) to approximately 1.7—3.4 times that of Witepsol S-55 and PEG 2000 suppositories.

In *in vivo* studies, as previously reported in rabbits, a large volume of secreted fluid was observed in the rectum and colon when PEG 2000 preparation was used.[21)] However, such a phenomenon was not observed for other preparations. Because Eudispert hv-hydrogels and xerogels are regarded as swellable and bioerodible matrixes, the drug release rate from gels depends on both rates of swelling and erosion, particularly on the added amounts of NaOH, the polymer concentrations and the drug distribution in gels. The larger amounts of sodium ion could be incorporated in Eudispert hv-hydrogels or xerogels by raising the amounts of sodium hydroxide over a range of 3 to 7 meq. Because an inner solution containing condensed sodium ion is separated from an outer water phase by a gel network-structure, the osmosis phenomenon may occur. When Eudispert hv-hydrogels or xerogels containing condensed sodium ions are immersed in a solution of lower osmotic pressure, the gels swell as water enters, and eventually the gel network-structure may become loose and water soluble compounds in the gels may be permeable to the outside. Consequently, the bioavailability of lidocaine for Eudispert hv-gels with 7 meq of sodium hydroxide increased compared with those for the gels with 5 meq of sodium hydroxide.

Fekete *et al.*[22)] and Lee *et al.*[23)] reported that methacrylic copolymer (Eudragit L) forms water insoluble complexes with some drugs containing amino or immino groups such as amitriptyline and propranolol. In the gastrointestinal tract, the drugs are released from these complexes slowly by an ion exchange process. The cationic drug (lidocaine) may react with the anionic polyelectrolyte (methacrylic acid copolymer) to form a sparingly soluble complex. Unfortunately, as the greater part of free methacrylic acid in Eudispert hv was neutralized with sodium hydroxide in this study, the existence of a complex formation between Eudispert hv and lidocaine HCl in the preparations could not be confirmed. Further study is needed to elucidate the possibility of the interaction and release mechanisms of drugs in these gel preparations.

We have reported in our previous papers[19,20)] that the use of PEG 2000 and Witepsol S-55 suppositories which were ascended from the opening of the anus by approximately 30 cm or more *via* the upper rectum to the colon at 5 h after administration in rabbit rectum makes it possible to bypass the liver first-pass metabolism of the drug only partially. This would coincide with the relatively poor bioavailabilities of lidocaine for these suppositories in the present study. However, Eudispert hv-hydrogel and xerogel preparations remain at the administration site, the lower rectum in rats and rabbits, over a fairly long period, because of the bioadhesive property of the gel itself, and they increase the bioadhesion of the gels to the rectal surface by absorbing the small volume of fluid in the rectum. Accordingly, the lidocaine absorbed may enter the lower and middle rectal vein and finally pass into the interior *vena cava*, bypassing the portal system and the liver, thereby improving the bioavailability of lidocaine by 8.7—12.8 folds compared with that for oral administration. Furthermore, the plasma concentraion pattern of lidocaine for rectal gel preparations was apparently sustained and prolonged compared with that for suppository preparations.

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