

Enhancing Effect of Glyceryl-1-monooctanoate on the Rectal Absorption of Gentamicin from Hollow-Type Suppositories in Rabbits¹⁾

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A hollow-type suppository containing gentamicin (GM) in its cavity was prepared using Witepsol H-15 (H-15) mixed with glyceryl-1-monooctanoate (MO) or MO alone in the body of the suppository (type I) and a suppository (type II) containing GM and MO in the cavity was constructed using H-15 in the body of the suppository.

Without MO, GM (60 mg) was not absorbed (plasma GM levels less than 1 µg/ml). However, the absorption of GM from the rectum of rabbits was enhanced by coadministered MO in types I and II. Even when the amount of GM was decreased to 6 mg (1/10), GM was observed in the plasma (C_{max} , 3.5 ± 0.3 µg/ml) after administration of the suppository made from MO mixed with H-15. The enhancing effect of MO on the rectal absorption of GM could not be further increased by incorporating an amount of MO larger than approximately 300 mg into the suppository.

This study demonstrates that MO can be used in the two types of hollow suppositories as an effective enhancing agent of rectal absorption of poorly absorbed drugs such as GM.

Keywords gentamicin; absorption enhancement; glyceryl-1-monooctanoate; medium-chain monoglyceride; hollow-type suppository; rectal delivery; rabbit

Recently, the enhancing effect of medium-chain glycerides (MCG)²⁾ on the absorption of poorly absorbed drugs from the intestine and rectum has been investigated. The medium-chain glyceride mixture MGK[®] (a commercially available preparation containing glyceryl monoctanoate, glyceryl dioctanoate, glyceryl trioctanoate, etc.) has been reported to have low oral and rectal toxicity³⁾ and to enhance rectal absorption of β -lactam antibiotics^{4,5)} and intestinal absorption of dyes.⁶⁾ Furthermore, glyceryl-1-monooctanoate (MO), a main component of MGK[®], significantly increased rectal absorption of cefmetazole sodium⁷⁾ and ceftioxin sodium⁸⁾ in rats.

The melting point of MO, an oleaginous base, is about 33–37°C, and it mixes well with some of the commercially available oleaginous suppository bases. MO is a convenient absorption-enhancing agent (absorption enhancer) to prepare suppositories containing poorly absorbed drugs.

In the present study, a hollow-type suppository⁹⁾ containing gentamicin (GM), a poorly absorbed antibiotic, in its cavity was constructed using Witepsol H-15 mixed with MO in the body of the suppository (type I), and a hollow-type suppository containing GM and MO in its cavity was prepared using Witepsol H-15 in the body of the suppository (type II). The enhancing effect of MO on the rectal absorption of GM in rabbits from these suppositories was evaluated.

Experimental

Materials GM (sulfate salt) was purchased from Sigma Chemical Co., St. Louis, MO, USA. MO (Poemu M-100[®]) was obtained as a gift from Riken Vitamin Co., Ltd., Tokyo, Japan. Witepsol H-15 (H-15, Hüls Troisdorf, Troisdorf, FRG) was used as the base. All reagents used were of analytical grade.

Preparation of Suppository with H-15 and MO The two types of hollow suppositories (Fig. 1) were prepared using H-15 and MO by the fusion-process method as described in our previous report.⁹⁾ Suppository type I (type I) containing GM in powder or aqueous solution form in its cavity was prepared from H-15 mixed with various amounts of MO or MO without H-15 in the body of the suppository. Suppository type II (type II) containing GM and MO (solid) in its cavity was constructed from H-15 without MO in the body of the suppository.

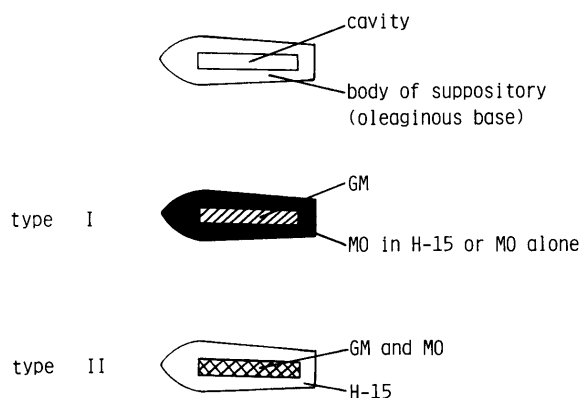


Fig. 1. Schematic Illustration of the Hollow-Type Suppositories Containing GM and MO

The weight of the suppository is about 2 g and the volume of the cavity is 0.5 cm³. Type I: amounts of GM are 6, 20 or 60 mg in the cavity and amounts of MO are 30, 90, 200, 300, 500 or 1000 mg in H-15 and MO alone (2000 mg) in the body of suppository. Type II: the amount of GM is 60 mg and the amount of MO is 30, 90, 200 or 300 mg in the cavity.

Animal Experiments and Assay of GM Male albino rabbits weighing 2.8–3.3 kg were fasted for one night prior to each experiment. They were allowed free access to water. The suppository was administered into the rectum according to the method described in our previous papers.^{9,10)} For intravenous bolus administration, GM dissolved in isotonic NaCl solution (20 mg/300 µl) was injected through the auricular vein at a dose of 20 mg. Blood samples were taken from the marginal ear vein at predetermined intervals after administration.

GM in plasma was assayed using an enzyme immunoassay (SLFIA)¹¹⁾ kit (Ames TDA[®], Ames Division, Miles Laboratories Inc., Elkhart, IN, U.S.A.).

Pharmacokinetic Analysis Pharmacokinetic parameters, the peak plasma GM concentration (C_{max}) and the area under the plasma concentration–time curves (AUC) were obtained from individual plasma GM concentration curves. The $AUC_{0-\infty}$ was estimated according to the trapezoidal rule, while extrapolation to infinity was carried out by dividing the last measured plasma GM level by the elimination rate constant (k_e), calculated from the terminal phase of the curve obtained by means of linear regression analysis. The extent of bioavailability (EBA) of GM was calculated as the ratio of the values of the mean $AUC_{0-\infty}$ obtained after rectal administration to those of the mean $AUC_{0-\infty}$ obtained after intravenous injection of GM.

For statistical evaluation of the results, the one-way ANOVA and the Dunnett's test were used. A *P*-value smaller than 0.05 was considered as significant.

Determination of Content of Water Absorbed in the Suppository Base An aliquot of 2 g of melted H-15 containing various concentrations of MO or MO alone was floated on water (approximately 4 ml) in the glass Petri dish (having about 30 cm² cross section) at a constant temperature (37°C). After being allowed to stand for 30 min, each sample was immediately solidified by rapid cooling of the water in the dish. The water on the surface of the solidified base materials was carefully removed, and the content of water absorbed was determined according to the Karl Fischer method using a Karl Fischer Moisture Meter (Model MK-AII, Kyoto Electronic Manufacturing Co., Ltd., Kyoto, Japan).

Results and Discussion

Plasma Concentration of GM after Rectal Administration of Hollow-Type Suppositories Containing Various Amounts of GM with 300 mg of MO in H-15 as the Body of Suppository To evaluate the rectal absorption of GM from the hollow-type suppository, type I containing 60, 20 or 6 mg of GM in its cavity and 300 mg of MO in H-15 as the body of the suppository (Fig. 1) was administered into the rectum of rabbits. Figure 2 shows the mean plasma GM concentration-time curves after rectal administration of type I containing the three different amounts of GM and after intravenous injection of 20 mg of GM. These pharmacokinetic parameters are summarized in Table I.

Without MO, GM (60 mg) in powdered form or aqueous solution was not absorbed (plasma GM levels less than

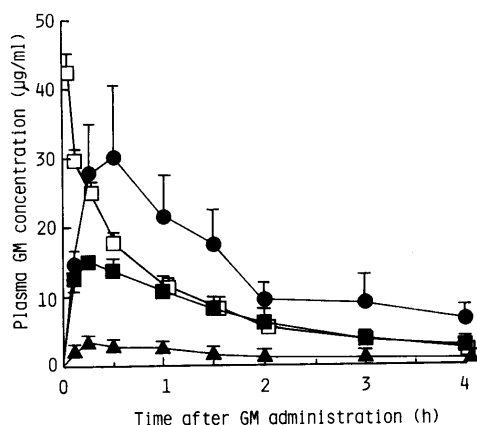


Fig. 2. Plasma Concentrations of GM in Rabbits Following Intravenous Injection (Open Symbols) or Rectal Administration (Closed Symbols) of the Type I Suppositories Containing 300 mg of MO in H-15 and Various Amounts of GM in the Cavity

Each point represents the mean \pm S.E. (vertical bar) of three rabbits for rectal administration or eight rabbits for intravenous injection. Amount of GM (mg): \bullet , 60; \square , 20; \blacktriangle , 6.

TABLE I. Pharmacokinetic Parameters of GM in Rabbits after Intravenous or Rectal Administration with MO

Adminis- tration	GM (mg)	C_{max} ($\mu\text{g/ml}$)	t_{max} (min)	k_{el} (h^{-1})	$AUC_{0-\infty}$ ($\text{h} \cdot \mu\text{g/ml}$)	EBA^a (%)
Intravenous ^b	20	—	—	0.61 ± 0.06	39.9 ± 2.0	100
Rectal ^c	60	31.3 ± 10.0	20 ± 5	0.33 ± 0.09	85.1 ± 25.4	71 ± 21
	20	15.3 ± 0.3	12 ± 3	0.40 ± 0.15	38.9 ± 9.7	97 ± 24
	6	3.5 ± 0.3	12 ± 3	0.41 ± 0.09	10.1 ± 2.8	84 ± 23

a) EBA (%) = $(AUC_{rectal}/AUC_{iv}) \times (D_{iv}/D_{rect}) \times 100$, *D* is the dose of GM; the subscripts rect and iv refer to rectal and intravenous administration, respectively. b) GM 20 mg/300 μl , bolus injection. c) Suppository, type I containing 300 mg of MO. Each value represents the mean \pm S.E. of eight rabbits for intravenous injection or three rabbits for rectal administration.

1 $\mu\text{g/ml}$).¹⁾ However, the absorption of GM from the rectum was significantly enhanced (C_{max} , $31.3 \pm 10.0 \mu\text{g/ml}$; $AUC_{0-\infty}$, $85.1 \pm 25.4 \text{ h} \cdot \mu\text{g/ml}$) by the coadministered MO. Even when the amount of GM was decreased to 6 mg (1/10), GM was observed in the plasma (C_{max} , $3.5 \pm 0.3 \mu\text{g/ml}$) after administration of the suppository made from MO in H-15. The k_{el} values of GM after rectal administration were not statistically different from that in the case of intravenous injection. Rectal delivery of 60, 20 or 6 mg of GM and 300 mg of MO in the cavity resulted in *EBA* values of $71 \pm 21\%$, $97 \pm 24\%$ and $84 \pm 23\%$, respectively. The differences among the mean values of *EBA* were not statistically significant.

In the previous paper,¹⁾ we reported that the enhancing effect of sodium salicylate (SA), an absorption enhancer, on the rectal absorption of GM in rabbits from the hollow-type suppository (type II) containing GM and SA was more efficient in the case of the powdered form than aqueous solution. In this study, the effect of the form of GM added in the suppository on the absorption-enhancing effect of MO was estimated with GM in powdered or solution form in the cavity of type I. Because it was impossible to prepare an aqueous solution containing GM and MO without a solubilizing agent, we did not examine type II. As shown in Fig. 3, no significant difference in plasma GM concentration-time curve profile was found between GM (60 mg) in powdered form and in aqueous solution (60 mg/400 μl) form in type I. Our results suggest that GM absorption is not influenced by GM concentration at the absorption sites in the rectum when GM is administered with MO.

Plasma Concentration of GM after the Coadministration of GM and Various Amounts of MO in the Suppository Type I or II To observe the absorption enhancing effect of MO, plasma GM levels were determined after the coadministration of GM (60 mg) and various amounts of MO in the type I or II suppository. The mean plasma GM concentration-time curves obtained with type I or II are illustrated in Fig. 4A and B, respectively. The $AUC_{0-\infty}$ values obtained are summarized as histograms in Fig. 5.

The GM absorption after rectal administration without

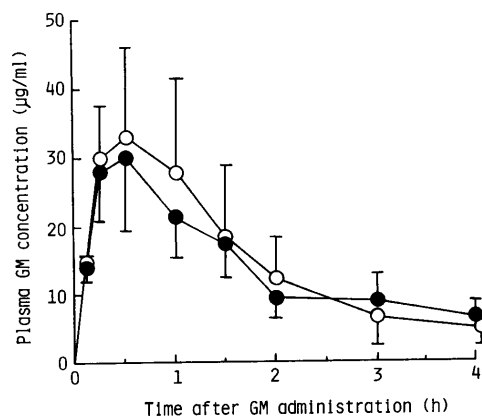


Fig. 3. Plasma Concentrations of GM in Rabbits Following Rectal Administration of the Type I Suppositories Containing 300 mg of MO in H-15 and 60 mg of GM in Powdered Form or Aqueous Solution in the Cavity

Each point represents the mean \pm S.E. (vertical bar) of three rabbits. Key: \bullet , powder (60 mg); \circ , solution (60 mg/400 μl (pH 6.8)).

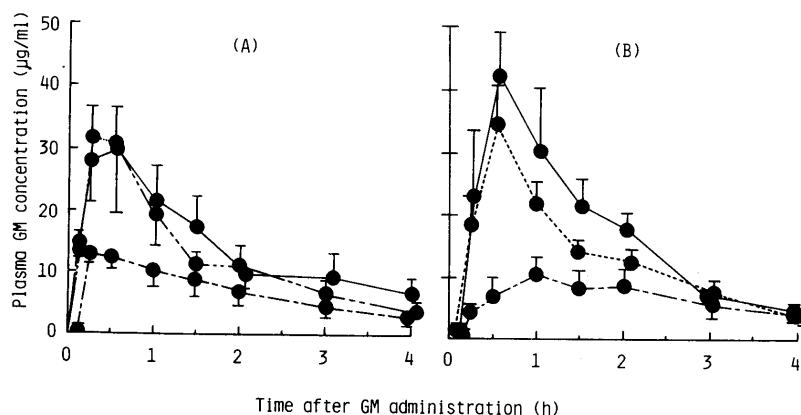


Fig. 4. Plasma Concentrations of GM Following Rectal Administration of the Hollow-Type Suppositories Containing 60 mg of GM with MO. Each point represents the mean \pm S.E. (vertical bar) of three rabbits. Suppository type: (A), I; (B), II. Amount of MO (mg): —, 0; - - -, 30; . . . , 90; — · — · , 2000.

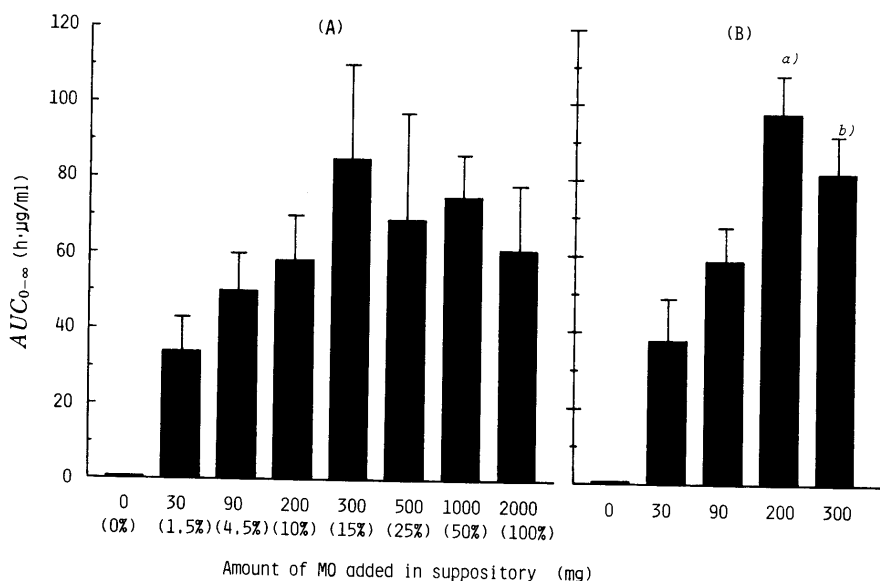


Fig. 5. AUC of GM in Rabbits Following Rectal Administration of GM (60 mg) and Various Amounts of MO. Suppository type: (A), I; (B), II. Statistically significant differences: a) $p < 0.01$ in 200 mg vs. 30 mg; b) $p < 0.05$ in 300 mg vs. 30 mg. The percentages shown in parentheses in Fig. 5 A present the concentration of MO in H-15 used to prepare type I. Each value represents the mean \pm S.E. of three experiments.

MO in the type I suppository was minimal, but it was significantly enhanced by coadministration of MO at 30 mg (C_{max} : type I, $12.3 \pm 1.9 \mu\text{g/ml}$; type II, $10.7 \pm 2.8 \mu\text{g/ml}$) or 300 mg (C_{max} : type I, $31.3 \pm 10.0 \mu\text{g/ml}$; type II, $42.0 \pm 7.0 \mu\text{g/ml}$) (Fig. 4). The $AUC_{0-\infty}$ values were increased by increasing amount of MO (MO 30 mg: type I, $33.6 \pm 9.0 \text{ h} \cdot \mu\text{g/ml}$; type II, $38.1 \pm 10.8 \text{ h} \cdot \mu\text{g/ml}$ and MO 300 mg: type I, $85.1 \pm 25.4 \text{ h} \cdot \mu\text{g/ml}$; type II, $81.9 \pm 10.4 \text{ h} \cdot \mu\text{g/ml}$).

Because the capacity of the cavity of the type II suppository used in this study was about 0.5 cm^3 , the amount of MO added in the cavity was restricted to approximately 400 mg. MO mixes well with H-15. Therefore, type I was used instead of type II for the experiments with larger amounts (above 400 mg) of MO. Two suppositories of type I were prepared from H-15 containing MO (amount, concentration: 500 mg, 25%; 1000 mg, 50%). Furthermore, type I containing the maximum amount (2000 mg) of MO (MO 100%) in the body of the suppository was prepared (Fig. 1). The GM absorption from these suppositories was evaluated. Concerning the handling of type I prepared from MO (100%) without H-15, insertion into the rectum should

be cautiously carried out, because this suppository is soft.

The plasma GM levels and the values of $AUC_{0-\infty}$ obtained from type I with 500, 1000 or 2000 mg of MO were not higher those obtained from the suppositories with 300 mg of MO (Fig. 5A), and the mean values of $AUC_{0-\infty}$ tended to decrease when large amounts (above 500 mg) of MO in type I were used. A similar result was observed with MO at 200 and 300 mg in type II (Fig. 5B).

For this reason, the enhancing effect of MO on the absorption of GM was maximal at approximately 300 mg. There may be an interaction between the suppository base containing large amounts (500–2000 mg) of MO and the rectal fluid, since MO has hydrophilic groups in its chemical structure. According to the determined content of water in H-15 containing various amounts of MO *in vitro* (Fig. 6), water was scarcely absorbed (less than 20 mg/g) by H-15 with MO at concentrations below 25% within 30 min. However, the content of water absorbed in H-15 with a high concentration of MO was quite large. Finally, the content of water absorbed by 100% MO was more than 200 mg. It is conceivable that a part of the rectal fluid would be mixed with H-15 containing a high concentration of

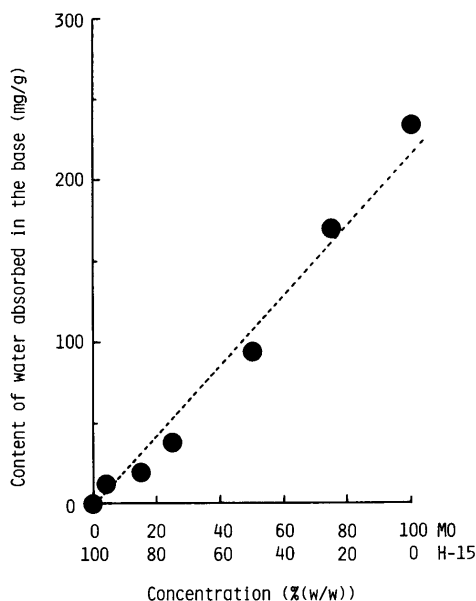


Fig. 6. Relationship between the MO Concentration in H-15 and the Content of Water Absorbed in H-15 Mixed with MO after Standing for 30 min on Water at 37°C

Each point represents the mean of three experiments.

MO, and consequently, GM absorption in the rectum would be decreased by the incorporation of GM dissolved in the rectal fluid into the base with high MO concentration. Our results are in general agreement with those for rectal absorption of cefmetazole sodium⁷⁾ in rats.

Interestingly, there was no statistically significant difference among the values of $AUC_{0-\infty}$ following use of MO at amounts from 30 to 2000 mg in type I, whereas the $AUC_{0-\infty}$ values following use of MO at 200 or 300 mg in type II were significantly higher than that obtained at 30 mg of MO. This may be because MO is released more rapidly from the cavity in type II than from the body of type I. Concerning the drug release from the cavity or the body (base material) of the suppository, we previously observed that drugs were dissolved more quickly from the cavity of the hollow-type suppository prepared using H-15 or another suppository base than from the conventional-type

suppository prepared using the same base material.^{9,12)}

This study demonstrates that MO in the two types of hollow suppositories can be used as an effective enhancing agent of rectal delivery of poorly absorbed drugs such as GM. In conclusion, GM is more efficiently absorbed in the presence of MO from type II than from type I, while type I is more convenient to prepare than type II, because type I can employ either powdered or aqueous solution form of GM in the cavity of the suppository.

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References and Notes

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