Oral Delivery of a Renin Inhibitor Compound Using Emulsion Formulations

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The oral delivery of *O*-(*N*-morpholino-carbonyl-3-L-phenylaspartyl-L-leucinamide of (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (I), a new renin inhibitor, was studied in the *in vivo* rat model using emulsion formulations. The components of the emulsion formulations were chosen based on their proposed effects on membrane structure, membrane fluidity, and solute transport. The percent absolute bioavailability (%AB) of I was increased from 0.3% (water suspension) to 5.1% when long-chain unsaturated fatty acid (oleic acid, linoleic acid, etc.)- and mono- and diglyceride (monolein, dilaurin, etc.)-containing emulsion formulations were used. Considering very high first-pass liver extraction of the compound (80%), it is suggested that emulsion formulations increased the intestinal transport of the compound significantly. The solubility of I in aqueous media with and without bile salt (20 m*M*) was found to be low (~1 μg/ml). Incubation in 0.01 *N* HCl did not affect the particle size of the emulsion. The titration of oleic acid/monoolein emulsion in a pH 6.5 medium with a mixed bile salt system indicated reduction in the particle size of the emulsion. Drug precipitation was observed above 30 m*M* bile salt concentrations. No drug crystals could be detected in the intestinal contents of the rats when emulsion formulations were ingested. These results suggest that in the intestine of the animals, the particle size of the emulsions is reduced in the presence of bile fluid while the drug resides primarily in the oil phase. The mechanism of enhanced transport of I from the emulsion formulations is discussed along with the possibility of cotransport for the drug and oil. Emulsion formulations can be a potential delivery form for low-bioavailable lipid-soluble drugs.

KEY WORDS: renin inhibitor; emulsions; oils; oleic acid; monoolein; oral delivery.

INTRODUCTION

Orally active renin inhibitors are promising in the treatment of hypertension (1); however, their low bioavailability has hampered formulation, clinical testing, and introduction into the market.

Past research in oral drug delivery has focused mostly on the physicochemical aspects of the drug molecules and formulations. In addition, future drug delivery technologies for peptide drugs must take advantage of biological absorptive mechanisms which transport large and small molecules into and out of cells.

Compound I [*O*-(*N*-morpholino-carbonyl-3-L-phenylaspartyl-L-leucinamide of (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane] (Scheme I) is a potent inhibitor specific for primate renin (IC_{50} for human renin is 5×10^{-8} *M*). Pharmacological studies in monkeys indicated very little absorption of this modified tripeptide compound in the intestine (2). In this study, several emulsion formulations were used to enhance the oral delivery of this renin inhibitor.

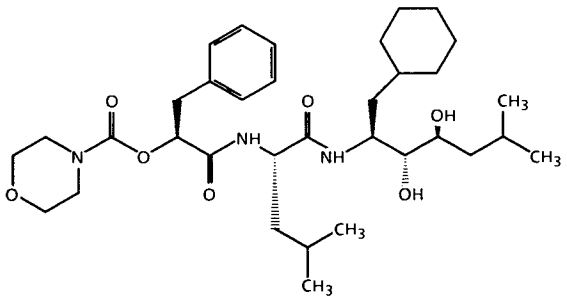
MATERIALS AND METHODS

Materials. Oleic acid (99%) and sodium taurocholate (NaTC) were obtained from Aldrich Chemical Co. (Milwaukee, WI). Sodium glycocholate, sodium glycochenodeoxycholate, sodium glycodeoxycholate, disodium glycolithocholate 3-sulfate, sodium taurochenodeoxycholate, sodium taurodeoxycholate, sodium taurolithocholic acid, disodium taurolithocholate 3-sulfate, monoolein (1-monooleoyl-rac-glycerol) (99%), palmitoyl-*dl*-carnitine chloride, dilaurin (50% 1,3 and 50% 1,2 isomers), monolaurin (1-monolauroyl-rac-glycerol) (99%), linoleic acid (99%), palmitoleic acid (99%), and caprylic acid (99%) were obtained from Sigma Chemical Co. (St. Louis, MO). Capmul MCM (mono-/diglycerides of caprylic/capric acids) was obtained from Capitol City Products (Columbus, OH). All the chemicals were used as supplied by the manufacturers.

Animal Studies. Male Sprague–Dawley rats were fasted for 18–24 hr prior to the experiments. In the oral studies, animals were dosed via gastric intubation. In the iv study, I (2 mg/kg) in PEG 400 (1 ml/kg) was delivered systemically through the tail vein. In the intraduodenal studies cannulas were surgically implanted into the duodenum, and the formulation was delivered to the conscious rats the next day using the cannula. Animals were bled from the tail vein or retroorbital at a 0.5- to 1-ml volume. When tail vein bleeding was used for blood sampling, an equivalent volume of saline was given to replace the lost blood. The animals were allowed to drink throughout the study but were allowed to eat only 3 or 8 hr following administration of the dose.

Data Analysis. The percent absolute bioavailability (%AB) values were calculated using the AUC (area under the plasma concentration–time curve) of the oral and iv doses as shown in Eq. (1).

$$\%AB = \frac{AUC^{oral} \times Dose^{iv}}{AUC^{iv} \times Dose^{oral}} \times 100 \quad (1)$$



Scheme I

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Plasma Analysis. Compound I levels in the plasma were analyzed by HPLC on a Waters 600 Multi Solvent Delivery System (Waters, Milford, MA) equipped with a Waters 712 (WISP) autosampler and a Kratos 783 Detector (IBI Analytical, Ramsey, NJ). A C18 NOVA PAK RCM column following a Brownlee guard column (RP-18, 10 μm, 3 cm × 4.6 mm, Brownlee Laboratories, Inc., Santa Clara, CA) was employed to separate the compounds, which were then detected at 210 nm. Switching was used to divert all late-eluting materials to waste. The mobile phase was acetonitrile:water (65:35, v/v), and the flow rate was 1 ml/min. Analysis began by thawing frozen plasma samples and centrifuging at 2000*g* at 4°C. The samples were extracted on a C18 Bond Elut column (Analytichem International, Inc., Bellefonte, PA) using acetonitrile. After solvent evaporation and reconstitution in the mobile phase, a 100-μl sample was injected into the HPLC. The calibration curves were obtained in the range of 0.01 to 2.0 μg/ml of compound.

Preparation of the Emulsions. Drug was dissolved in the oil and the sodium taurocholate (NaTC) (0.5%, w/w) was dissolved in the water phase. The mixture of oil (32%, w/w) and water (68%, w/w) phases was sonicated using a tissue disrupter (Tekmar sonic disrupter, Tekmar Co., Cincinnati, OH) for about 3–5 min. In the preparation of the emulsions containing mono- and diglycerides, oleic acid was employed at a 20% (w/w) and glycerides were employed at a 12% (w/w) level. In the oleic acid/palmitoyl carnitine (0.5%, w/w) emulsion, NaTC was excluded since stable emulsions could not be prepared. All emulsions were prepared within 24 hr of the animal experiments.

Photon Correlation Spectroscopy. Each emulsion sample was mixed in a vortex mixer for 10 sec. One drop of emulsion was mixed with 20 ml of filtered (0.45 μm) water. The resulting solution was sonicated for 20 sec in a sonic bath. Approximately, 3 ml of this solution was transferred to the light-scattering cell of the geniometer (Brookhaven Instruments Model BI-160). The geniometer had previously been equilibrated at 30°C. After 15 min of equilibration, light scattering from a 5-mW helium/neon laser was measured at 90° using an autocorrelator (Brookhaven Instruments Model BI-2030). The particle size reported in this paper was determined by a second cumulant data program in the autocorrelator. Five- to tenfold dilution of an oleic acid/monoolein emulsion with water before the measurements did not make any significant change in the oil droplet sizes.

Microscopy. A drop of the emulsion was placed between a coverslip and a glass microscope slide. The slides were examined in transmitted, polarized light. Oil droplets were sized by aligning them with a calibrated reticle in the microscope ocular.

Solubility Measurements. The solubility limit measurements, except in water and bile salt media, were conducted using a gravimetric method. For the solubility measurements in water, drug suspensions (with and without NaTC) were stirred overnight at room temperature. The clear supernatant resulting from the centrifugation and filtration of the mixture was analyzed by HPLC.

Titration of Emulsions with Bile Salts. Appropriate amounts of oleic acid/monoolein emulsions (with and without I) were mixed with 0.1 *M* phosphate buffer (pH 6.5) to achieve a 1 g/dl final oil concentration. A solid bile salt mixture (Table I) was then gradually added and the dispersions were examined by microscopy and photon correlation spectroscopy.

Physical State of the Emulsions in the Intestine. Drug containing (20 mg/ml) oleic acid/monoolein and caprylic acid/Capmul MCM emulsions were delivered at 1 ml/kg into the stomach of the fasted rats. One animal was sacrificed at 1 hr and another at 2 hr for each emulsion along with a control animal which did not receive any formulation. The stomach and small intestinal contents were washed out separately with 2 ml of distilled water. These were then examined under light microscope for the presence of oil droplets and drug crystals.

RESULTS AND DISCUSSION

The solubility of I in water is very low (Table II). Further, in the micellar solution of bile salt the aqueous solubility of the compound did not improve. The oral administration of I in a simple water suspension resulted in low plasma levels and only approximately 0.3% absolute bioavailability (Fig. 1 and Table III). Following injection of the compound into the portal vein, first-pass liver extraction of I was above 80% (data not shown). Based on these results, it was suggested that the low bioavailability of I in rats may be due to its low solubility in the intestinal medium, high first-pass liver extraction, and limited transport through the mucosa.

The solubility of I in the unsaturated liquid fatty acids with and without mono- and diglycerides is high (Table II). Such formulations could provide the dose needed for therapeutic activity. The other advantage of unsaturated fatty acids with mono- and diglycerides in formulations is that they are membrane adjuvants. Most unsaturated fatty acids and monoglycerides cause membrane fusion and affect the fluidity of the lipid membrane (3,4). These molecules have been shown to enhance the intestinal absorption of small- and large-size molecules with different lipophilicities (5–8). Diglycerides, by stimulating protein kinase in the enterocytes, may affect the permeability of the paracellular junctions (9–11).

The use of emulsion-type oil dispersions in drug delivery is not new. The surface area of oil droplets in emulsion formulations is significantly increased, which enhances the mucosal uptake of drugs from the emulsion formulations. In this study several classes of emulsions were developed, characterized, and orally tested in rats. The droplet size of

Table I. Composition of Mixed Bile Salt System

Species	Mol%
Sodium glycocholate	24
Sodium glycochenodeoxycholate	24
Sodium glycodeoxycholate	16
Disodium glycolithocholate sulfate	3
Sodium taurocholate	12
Sodium taurochenodeoxycholate	12
Sodium taurodeoxycholate	8
Sodium taurolithocholate	0.3
Disodium taurolithocholate sulfate	1

Table II. Solubility of Compound I in Various Media[a]

Media	Solubility (mg/ml)
Oleic acid	>200
Monoolein	>100
Oleic acid/dilaurin	>53
Oleic acid/monoolein	>53
Linoleic acid	>63
Palmitoleic acid	>63
Caprylic acid	>63
Octanol	>4
Water	0.0010
20 m*M* NaTC in water	0.0011

[a] At least two measurements were performed in each case.

oil globules in the emulsion formulations were all less than 1 μm (Table III). A few larger oil globules were also detected (up to 15 μm) under a microscope. No birefringence could be seen in any of the emulsions under cross polarizers of the light microscope.

As shown in Fig. 1, the oral absorption profiles of I from oleic acid and monoolein solutions appear different. The oleic acid solution has a C_{max} at 8 hr, while the monoolein solution has a C_{max} at approximately 3 hr. Oleic acid in the form of an emulsion produced a plasma concentration–time profile which was similar to that of the monoolein solution (Fig. 2). The results with the palmitoleic acid and linoleic acid emulsions were similar to those obtained with the oleic acid emulsion (Fig. 2 and Table III). In another experiment, the oleic acid emulsion was delivered directly into the duodenum. The results showed that there was no significant difference in either the blood–concentration profile (data are not shown) or the absolute bioavailability values (Table III). These results are consistent with the *in vitro* experiments in which the dilution of oleic acid/monoolein (1 or 7 parts) emulsion in 0.01 *N* HCl (100 parts) neither affected the droplet size of the emulsion nor caused formation of drug crystals assessed by microscopy. Similar results were obtained when caprylic acid/Capmul MCM emulsion was used. These observations suggest that stomach emptying and/or acid secretion in the animals may not be critical in the absorption of I from the oleic acid emulsion.

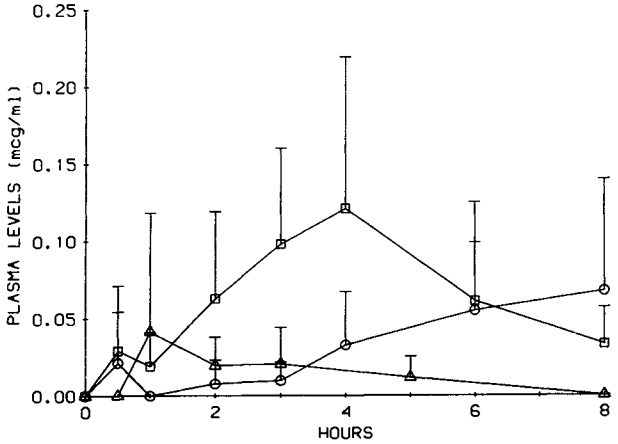

Fig. 1. Plasma concentrations of I as a function of time following oral administration of water suspension (△), oleic acid solution (○), and monoolein solution (□) at 20 mg/kg.

In the next series of formulations, emulsions containing oleic acid/monoolein, oleic acid/monolaurin, oleic acid/dilaurin, oleic acid/palmitoyl carnitine, and caprylic acid/Capmul MCM were tested for their ability to enhance the oral delivery of I. Palmitoyl carnitine was used because of its effect on membrane fluidity and drug absorption (12). Further, a ratio of oleic acid to mono- or diglyceride of approximately 2:1 was used since it is consistent with the levels seen in the intestine after a fatty meal (13,14). At this level of glycerides stable emulsions with small particle sizes could be prepared (15). In Figs. 3 and 4, the plasma concentration–time profiles of these emulsions indicate that the oleic acid/dilaurin formulation produced the highest plasma concentration and percent absolute bioavailability (%AB). However, because of the variability in the data there was no statistical difference in either the %AB or the plasma concentrations corresponding to the above formulations, except with the caprylic acid/Capmul MCM emulsion. Based on 80% first-pass extraction of the compound in the liver, a 3–5% AB value indicates that more than 20% of the compound is transported into the portal vein.

The mechanism of drug absorption from an oil solution is not well understood. If a drug dissolved in oil can partition into the aqueous phase in the intestine, then the absorption can proceed by usual mechanisms (16). However, if a drug, such as I, has very limited solubility in an aqueous medium even in the presence of bile salt (Table II), then the mechanism of drug uptake from the oil formulations may not be limited just to uptake from the aqueous phase in the intestine.

It has been shown that humans can absorb 50–75% of the administered fatty meal in the absence of bile fluid (17). Therefore, the possibility of direct fusion of liquid crystalline lipid phases with the membrane during lipid transport was implicated (18–20). Recent studies indicate that dietary lipids and lipolysis products in the intestine can exist in the viscous isotropic phase (cubic phase), vesicular, hexagonal, lamellar liquid crystalline, oil globule, regular and inverse (L2-phase) micellar phases (18–21). The presence of such phases in the intestine depends on the type and levels of the lipid components (14). During fusion of lipids with membrane, chemicals dissolved in the lipid phase can be taken up into cells.

In an attempt to understand the physical state of the emulsions in the intestine, two experiments were performed. In the *in vitro* experiments oleic acid/monoolein emulsion was titrated with a mixed bile salt system of a composition similar to that of human bile (Table I). The droplet size of both the blank and the drug-containing emulsions decreased almost linearly, from ~300 to 150 nm, as the concentration of bile salts was increased from 0 to 45 m*M*. Microscopic examinations of the drug containing mixtures indicated precipitation of the drug at bile salt concentrations above 30 m*M*. This result indicated that droplet size was not affected by the precipitation phenomena. In an *in vivo* experiment, oleic acid/monoolein and caprylic acid/Capmul MCM emulsions were administered into the stomach of the rats. Microscopic examination of the stomach and intestinal contents of

Table III. Percent Absolute Bioavailability (%AB) of Compound I from Various Formulations at a 20-MPK Dose

Formulation	Particle size (μm)[a]	Volume administered (ml/kg)	Number of animals	%AB (mean ± SD)
iv solution[b]				100
Water suspension		10	8	0.35 ± 0.37
Oils				
Oleic acid		1	4	1.57 ± 1.06
Monoolein		0.5	4	3.32 ± 1.07*
Emulsions				
Oleic acid	0.645	1	8	3.74 ± 1.74*
Linoleic acid	—	1	7	3.52 ± 1.47*
Palmitoleic acid	0.806	1	8	3.29 ± 1.54*
Oleic acid/monoolein	0.264	1	11	3.30 ± 1.30*
Oleic acid/monoolein[c]	—	10	8	3.90 ± 2.45*
Oleic acid/monoolein[d]	—	1	8	2.30 ± 0.94*
Caprylic acid/Capmul MCM	—	1	8	1.20 ± 1.10
Oleic acid/monolaurin	0.280	1	8	4.79 ± 1.66*
Oleic acid/dilaurin	0.251	1	8	5.10 ± 2.18*
Oleic acid/palmitoyl carnitine	0.561	1	8	4.60 ± 1.96*

[a] The reported values are the average of at least two measurements which showed less than 10% variation.
[b] The total AUC value is 2.41 (μg/ml) × hr. The k_{el} (beta phase) is 0.93 hr^{-1}. In all the %AB calculations 0- to ∞-time total AUC values were used.
[c] The emulsion was prepared at a 10 ml/kg volume using 10 times more oil. Other emulsions listed at a 1 ml/kg volume were diluted with water to 10 ml/kg before delivery.
[d] Intraduodenal rat model was used.
* Significantly different from water suspension at $P < 0.001$ using Student's t test.

the animals at 1 and 2 hr revealed a pattern similar to that of the control animal (no emulsion). The gastrointestinal (GI) contents of both the control and the emulsion-injected animals contained oil droplets. No obvious drug crystals could be detected in the GI contents of the emulsion injected animals. These results are consistent with the results of the *in vitro* dilution experiments. The bile salt concentration in the intestine of the rats is below 20 m*M* (16), and one would not expect any precipitation of the drug in the intestine. These results and earlier solubility measurements indicate that I is dissolved primarily in the oil phase in the intestine of the animals. The cotransport of lipid and drug across the brush border membrane (through a fusion mechanism) may at least partially explain the enhanced transport of drug from the emulsion formulations.

The dependence of I absorption on the oil volume is consistent with an oil–drug cotransport mechanism (Fig. 5). In the 1 ml/kg emulsion, the concentration of the drug in the lipid phase is 10 times greater than the concentration in the

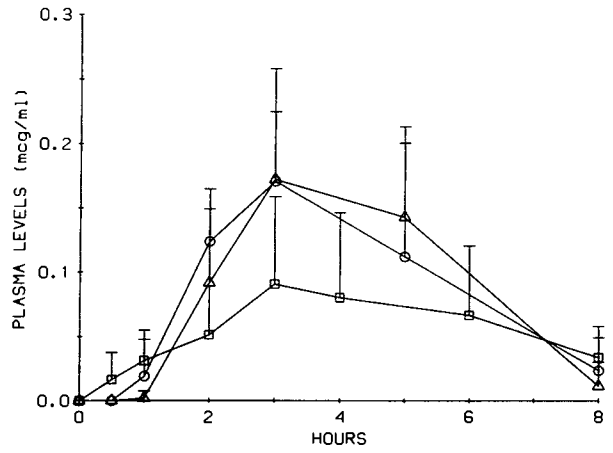

Fig. 2. Plasma concentrations of I as a function of time following oral administration of oleic acid (○), palmitoleic acid (△), and linoleic acid (□) emulsions at 20 mg/kg.

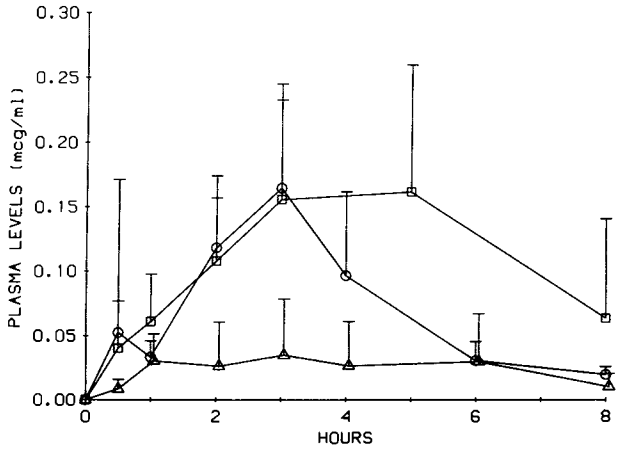

Fig. 3. Plasma concentrations of I as a function of time following oral administrations of oleic acid/monoolein (○), oleic acid/monolaurin (□), and caprylic acid/Capmul MCM (△) emulsions at 20 mg/kg.

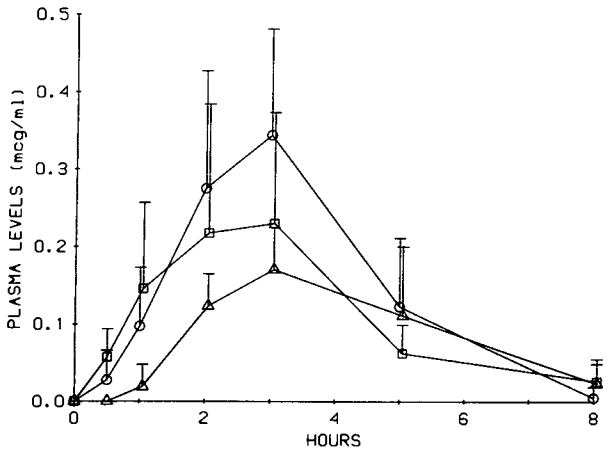

Fig. 4. Plasma concentrations of I as a function of time following oral administrations of oleic acid (△) (same as shown in Fig. 2 without the 24-hr point), oleic acid/dilaurin (○), and oleic acid/palmitoyl carnitine (□) emulsions at 20 mg/kg.

10 ml/kg emulsion. When administered, the concentrated emulsion (1 ml/kg) produced significantly higher plasma levels of I at 3 hr compared to the 10 ml/kg emulsion. Such concentration-dependent transport of drugs from emulsions was also observed by other investigators using marker dyes which were soluble primarily in the oil phase (22). Further studies are necessary to substantiate the validity of a lipid–drug cotransport mechanism.

The enhanced transport of I from some of the emulsion formulations may be due to favorable interaction of some of the oils with the membrane, which leads to enhanced drug permeability across the brush border membrane. The physical state of the liquid crystalline oils at the vicinity of the mucosa may also be important in a possible cotransport mechanism for oils and drugs. Any hydrolytic degradation of the drug in the gastrointestinal tract should also be prevented by use of oil dispersions because of the high drug solubility in the oil phase of the formulations (23).

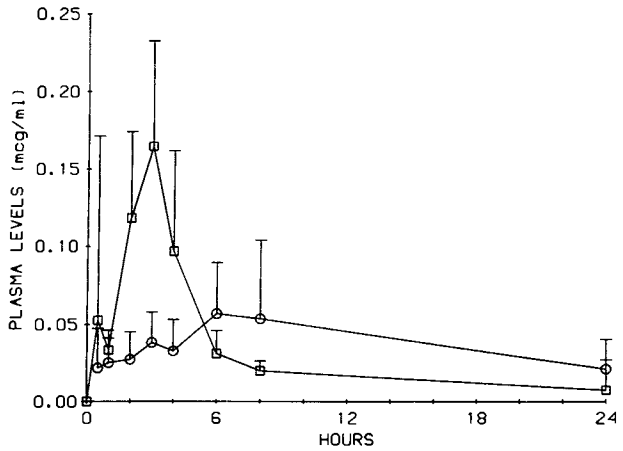

Fig. 5. Plasma concentrations of I as a function of time following oral administration of oleic acid/monoolein emulsions, (□) 1 ml/kg (same as shown in Fig. 3 with the added 24-hr point) and (○) 10 ml/kg at 20 mg/kg.

The oleic acid/monoolein emulsion formulation also increased the absolute bioavailability of I upon nasal administration in the rat (24). In conclusion, the emulsion formulations containing oil components that are membrane adjuvants can be used to enhance oral delivery of peptimimetic drugs.

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