Furosemide Pharmacokinetics and Pharmacodynamics following Gastroretentive Dosage Form Administration to Healthy Volunteers

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The objective of this study was to evaluate the pharmacokinetic and pharmacodynamic properties of furosemide following gastroretentive dosage form (GRDF) administration. A furosemide (60 mg) GRDF, releasing the drug during 6 hours in vitro, or an immediate-release tablet was administered to healthy male volunteers (N = 14) in a crossover design. Food and liquid intake were standardized; urine was collected, weighed, and assayed for furosemide and sodium concentrations. Pharmacokinetics of furosemide following the GRDF administration, as compared to the tablet, showed lower $C_{\text{max}}$ and indicated a prolonged absorption phase leading to longer mean residence time in the stomach. The sustained input of the drug significantly improved diuretic and natriuretic efficiencies during the first 5 hours and thereby increased the total effects measured over 24 hours. The unfolding controlled-release GRDF of furosemide improved the pharmacodynamic actions due to the sustained absorption in the stomach and jejunum, which delayed the body’s counteractivity to the drug effect.

**Keywords:** Furosemide; gastroretentive; humans; pharmacokinetics; pharmacodynamics; controlled release

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Furosemide, a widely used “high-ceiling” loop diuretic drug, is indicated for congestive heart failure, chronic renal failure, and hepatic cirrhosis. Furosemide is absorbed mostly in the stomach and upper small intestine, possibly due to its weak acidic properties (pKa 3.9), and is characterized by a short half-life of 1.3 ± 0.8 hours (mean ± SD). The narrow absorption window of furosemide leads to its low bioavailability (49% ± 17%, mean ± SD).

A major problem with furosemide oral pharmacotherapy is dissipation of the natriuretic effect before the next dose of the drug is given. During this interval, due to the osmoregulation and volume regulation, the rebound sodium retention in the nephron might significantly decrease the prior natriuresis. Administration of furosemide as an intravenous infusion was previously shown to improve its diuretic and natriuretic activities in comparison to a bolus injection. This dependency of the furosemide effect on the mode of drug administration provides an explanation for the equipotent diuretic and natriuretic effects of controlled-release and immediate-release (IR) dosage forms, despite the significantly lower bioavailability of the controlled-release tablets.

The narrow absorption window of furosemide in the upper part of the gastrointestinal tract, together with the improved effect of continuous drug input, provides a rationale for developing a gastroretentive dosage form (GRDF) for this drug. Such a dosage form would be re-
tained for prolonged periods of time in the stomach and release the drug in a sustained manner, thus providing the drug continuously to its absorption sites in a controlled manner, extending the absorption phase and increasing the magnitude of the drug effect. Two types of GRDFs have been previously developed for furosemide and apply different approaches: low-density floating tablet or mucoadhesive microspheres. Both GRDFs increased the bioavailability of furosemide in animal12 or human studies.13,14 However, the pharmacodynamic effect was either not measured12,13 or diminished.14

The objective of the current study is to evaluate the pharmacokinetics and the pharmacodynamics of a novel GRDF of furosemide in comparison to the IR tablet in healthy volunteers. This GRDF platform is based on an unfolding multilayer polymeric system15 and was previously shown (1) to be retained in the stomachs of dogs and humans for prolonged periods of time (≥ 5 h)16,17 and (2) to enhance the bioavailability and extend the absorption phase of riboflavin16 and levodopa18 in comparison to nongastroretentive controlled-release dosage forms in dogs.

METHODS

GRDF Preparation

The preparation of the novel GRDF has been described elsewhere.15-18 In brief, a multilayer (sandwich-type) polymeric GRDF was composed of an inner layer that contained 60 mg of furosemide dispersed in a degradable polymeric membrane that was framed with rigid polymer strips covered on both sides by two outer degradable polymer membranes. The rigid strips contained radiopaque contrast threads. The membranes were attached to each other using minute amounts of ethyl alcohol. The dimensions of the GRDF were 5.5 × 2.1 × 0.07 cm (length, width, and thickness, respectively), and it was folded into a gelatin capsule (00) prior to in vitro and in vivo evaluation.

In Vitro Evaluation of Drug Release

The release kinetics of furosemide from the control IR tablet and the GRDF into phthalate buffer (pH 4.6, NaOH-phthalate) was conducted using USP 23 apparatus 2 at 37°C (100 rpm, Caleva ST7, Dorset, UK). The drug concentration was determined by UV absorption at 332 nm applying appropriate calibration curves.

Subjects

The study followed the tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the Ethics Committee of the National Medical Center, Budapest, Hungary. The volunteers gave their informed consent to participate in the study. The health of the volunteers (male Caucasians, N = 14; age, 34 ± 7; weight, 78 ± 12 kg; mean ± SD) was ascertained according to detailed medical history, SMAC biochemical and hematological laboratory evaluation, and physical examination. None of the volunteers used medications regularly.

Study Design

The volunteers received two dosage forms of 60 mg furosemide in a randomized crossover design: IR tablet (Furosemid®, Chinoi, Budapest, Hungary) and a GRDF. The administration was performed at 8:00 a.m. following an overnight fast, with 200 mL water and a sandwich (325 Kcal). Food and fluid intake were standardized according to a strict protocol: a sandwich (325 Kcal), two cakes (480 Kcal), and a standard meal were provided at 5, 8, and 12 hours postadministration, respectively. The water intake was 250, 250, and 400 mL at 5, 8, and 12 hours postadministration, respectively. Urine was collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 hours postadministration; the sample volume was determined by weighing; and the samples were frozen (–20°C). Following each urination, the volunteers received 100 mL of the rehydration solution (Hydran®, Teva Pharmaceutical Industries, Kfar-Sava, Israel) containing the following: sodium, 64.3 mmol·L⁻¹; potassium, 20.0 mmol·L⁻¹; citrate, 10.0 mmol·L⁻¹; chloride, 54.3 mmol·L⁻¹; dextrose, 166.5 mmol·L⁻¹. The washout period between the phases was 7 days.

Furosemide urine concentrations were determined by a high-performance liquid chromatography (HPLC) method that has been described previously.19 An X-ray picture was taken 5 hours following furosemide-GRDF administration to evaluate its location in the gastrointestinal tract.

Pharmacokinetic Model

A two-compartment model with lag time was applied to describe the pharmacokinetics of furosemide. The average furosemide excretion rate versus time follow-
ing administration of the GRDF or IR tablet was analyzed, and the pharmacokinetic parameters were determined, assuming that the furosemide excretion rate was directly proportional to the drug concentration in the central compartment. The differential equations used to describe the pharmacokinetic model were as follows:

\[ \frac{dX_g}{dt} = -k_a \cdot X_g, \quad (1) \]
\[ \frac{dX_p}{dt} = k_a \cdot X_g - (k_{10} + k_{12}) \cdot X_p + k_{21} \cdot X_t, \quad (2) \]
\[ \frac{dX_t}{dt} = k_{12} \cdot X_p - k_{21} \cdot X_t, \quad (3) \]

where \( X_g, X_p, \) and \( X_t \) are the drug amounts in the gastrointestinal tract and the central and peripheral compartments, respectively. The rate constants are as follows: \( k_a \) is the absorption from the gastrointestinal tract to the central compartment, \( k_{10} \) is the elimination from the body, \( k_{12} \) is the transfer from the central to the peripheral compartment, and \( k_{21} \) is the transfer from the peripheral to the central compartment. These parameters, together with the lag time \( (t_{lag}) \) and the volume of distribution \( (V) \), were later used as input for the pharmacodynamic modeling.

**Pharmacodynamic Models**

Several modeling approaches were applied to analyze the diuresis and natriuresis data following furosemide administration as GRDF or IR tablets, including the direct and indirect response models with different mechanisms of tolerance development.\(^{20,21}\)

The final model assumed that a direct relationship existed between the furosemide excretion rate and the pharmacodynamic data. The observed drug effect was assumed to be produced by two mechanisms, one of which was subject to tolerance development according to the following equations:

\[ E = E_0 + E_1 + E_2/M, \quad (4) \]
\[ E_1 = \frac{E_{max1} \cdot \left(ER\right)^{n_1}}{(EC_{501})^{n_1} + \left(ER\right)^{n_1}}, \quad (5) \]
\[ E_2 = \frac{E_{max2} \cdot \left(ER\right)^{n_2}}{(EC_{502})^{n_2} + \left(ER\right)^{n_2}}, \quad (6) \]

where \( E \) is the observed effect (diuresis or natriuresis); \( E_0 \) is the basal response; \( E_1 \) and \( E_2 \) are the two components of the drug effect; \( M \) is the concentration of the modifier that caused tolerance development; \( E_{max1} \) and \( E_{max2} \) are the maximal effects; \( ER \) is the furosemide excretion rate \( (ER = X_p/V) \); \( EC_{501} \) and \( EC_{502} \) are the drug concentrations that produce 50\% of \( E_{max1} \) and \( E_{max2} \), respectively; and \( n_1 \) and \( n_2 \) are the shape factors. For simplicity, the concentration of the modifier \( M \) was assumed to be 1 at the time of drug administration. At time points when the furosemide excretion rate was higher than the critical value \( (ER_{crit}) \), the modifier concentration was assumed to increase according to the following equation:

\[ \frac{dM}{dt} = k_{tol}, \quad (7) \]

where \( k_{tol} \) is the zero-order rate constant of tolerance development.

**Pharmacokinetic and Pharmacodynamic Analysis**

At the first stage, the pharmacokinetic model was fitted to the mean furosemide excretion rate versus time data following administration of the GRDF or IR tablet, and the pharmacokinetic parameters were determined. At the next stage, the pharmacodynamic model was fitted to the mean diuresis or natriuresis versus time data using the estimated pharmacokinetic parameters as fixed values. For each of the measured outcomes (diuresis or natriuresis), the pharmacodynamic analysis was performed simultaneously for the GRDF and IR tablet data sets.

The modeling was performed using ADAPT II software (Biomedical Simulations Resource, Los Angeles), applying the generalized least squares procedure.\(^{22}\) The variance was described by the following linear model:

\[ \text{Var} R = (a + b \cdot R)^2, \quad (8) \]

where \( a \) and \( b \) are the variance parameters. Goodness of fit was determined according to Akaike (AIC) and Schwarz (SC) criteria.\(^{21}\)

The fraction absorbed versus time plot was calculated from the furosemide urine excretion versus time data according to the Wagner-Nelson method.\(^{23}\) The elimination rate constant that was required for this method was calculated as the linear terminal slope of the furosemide urinary excretion rate versus time curve.

Mean residence time (MRT) was calculated from excretion data, assuming that the fraction excreted unchanged \((fe)\) remained constant over time.\(^{24}\)
The diuretic and natriuretic efficiencies over a certain time period were calculated according to the following equations:

\[
\text{Diuretic efficiency } U_{t} = \frac{U_{0} - t}{A_{0} - t}, \quad (9)
\]

\[
\text{Natriuretic efficiency } \frac{Na_{0} - t}{A_{0} - t}, \quad (10)
\]

where \(U_{0} - t\), \(A_{0} - t\), and \(Na_{0} - t\) are the total urine (mL), drug (mg), and sodium (mmol) amounts excreted, respectively, from the administration time until a specific time point \(t\).

**Statistical Analysis**

The two-tailed \(t\)-test was used to assess the statistical significance of the differences between the experimental groups. A \(p\)-value of less than 0.05 was termed significant. Data are presented as mean \(\pm\) SEM, except when stated otherwise.

**RESULTS**

Furosemide was gradually released from the GRDF in vitro during 6 hours (Figure 1). The X rays showed that 5 hours postadministration, the GRDF was still in the stomach of 9 volunteers out of 14. Diuresis and natriuresis data of individual subjects during 0 to 24 hours after the drug administration are presented in Table I. In most subjects, the data followed the same trend, and the GRDF administration yielded higher diuresis and natriuresis compared to the IR dosage form.

The parameters related to the furosemide, urine, and sodium excretion following the administration of the studied furosemide dosage forms are presented in Table II. It can be seen that the GRDF, as compared to the IR tablet, was characterized by a lower maximal furosemide excretion rate, a longer time to the maximal furosemide excretion rate, a higher MRT, a higher maximal diuresis (diuretic rate), a longer time to maximal diuresis and natriuresis (natriuretic rate), a lower furosemide excretion but higher diuretic and natriuretic efficiencies during the first 5 hours, and higher cumulative diuretic and natriuretic effects over the 24 hours postadministration.

The effect of the dosage form on the urinary excretion rate of furosemide is shown in Figure 2a. It can be seen that the GRDF yielded lower, flatter, and extended excretion rates. The two-compartment pharmacokinetic model with lag time appropriately described the time course of the furosemide excretion rate. The estimated pharmacokinetic parameters for both the GRDF and IR dosage form are presented in Table III. According to the Wagner-Nelson plot showing the fraction of dose absorbed versus time, the GRDF prolonged the absorption phase of furosemide from 2 hours to 6 hours (see Figure 2b).

The effect of dosage form type on diuresis and natriuresis (Figure 3) shows that the GRDF produced higher diuresis than IR tablets for a period of about 7 hours. Natriuresis versus time curve profiles had a similar pattern for both dosage forms, but onset and duration of sodium excretion were somewhat delayed for GRDF compared to the IR tablet.

The pharmacokinetic-pharmacodynamic curves for both diuretic and natriuretic effects following administration of 60 mg furosemide by the two studied modes of administration are presented in Figure 4a and 4b, respectively. It can be seen that during the first hours, the slow input of the drug from the GRDF yielded a significantly superior magnitude of diuretic and natriuretic effects. Later, the body homeostatic responses appear to have been activated, leading to tolerance development (exhibited on the graph as a clockwise hysteresis). For

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diuresis (mL)</th>
<th>Natriuresis (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GRDF</td>
<td>IR Tablet</td>
</tr>
<tr>
<td></td>
<td>GRDF</td>
<td>IR Tablet</td>
</tr>
<tr>
<td>1</td>
<td>3171</td>
<td>2173</td>
</tr>
<tr>
<td>2</td>
<td>3323</td>
<td>2340</td>
</tr>
<tr>
<td>3</td>
<td>4880</td>
<td>2232</td>
</tr>
<tr>
<td>4</td>
<td>3360</td>
<td>2657</td>
</tr>
<tr>
<td>5</td>
<td>3830</td>
<td>1873</td>
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<td>6</td>
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<td>9</td>
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<td>10</td>
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<td>11</td>
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<td>2144</td>
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<td>2911</td>
<td>2623</td>
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<tr>
<td>14</td>
<td>2594</td>
<td>2565</td>
</tr>
<tr>
<td>Mean</td>
<td>3169*</td>
<td>2281</td>
</tr>
<tr>
<td></td>
<td>276*</td>
<td>215</td>
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<td>SEM</td>
<td>221</td>
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<tr>
<td></td>
<td>25</td>
<td>13</td>
</tr>
</tbody>
</table>

*Significantly different from IR tablet, \(p < 0.05\).
the IR tablet, the homeostatic responses appear to be activated much earlier, leading to the differences in the shape of the diuretic and natriuretic pharmacokinetic-pharmacodynamic curves for the studied dosage forms. Consequently, the GRDF produced a substantially higher maximal diuretic rate compared to the IR dosage form. On the other hand, the maximal natriuretic rates were similar for both dosage forms.

We have tried to adopt the pharmacodynamic models that were previously designed to describe the furosemide activity time course, including tolerance development. However, these models did not provide an appropriate description of the observed diuresis and natriuresis data following administration of the GRDF and IR dosage forms. On the other hand, the direct response model that considers two components that produce the drug effect, one of which was subject to tolerance (see equations (4)-(7)), described appropriately the main trends of the diuresis and natriuresis following administration of the studied dosage forms (see Figure 3). The estimated pharmacokinetic parameters for both GRDF and IR dosage forms are presented in Table 4.

Individual data show no correlation between the overall natriuretic effect and the total furosemide amount excreted after 24 hours for each of the studied dosage forms (see Figure 5; similar outcomes were observed for the diuretic effect). The slope of the linear correlation between the two pharmacodynamic measurements (diuretic and natriuretic rates) was significantly different for the studied dosage forms ($p < 0.05$) (see Figure 6). No adverse effects were noted due to GRDF administration, whereas 1 volunteer suffered from nausea and vomiting 8 hours after IR tablet administration.

### Table II Average Furosemide, Urine, and Sodium Excretion Parameters (mean ± SEM) following Administration of 60 mg Furosemide as Gastroretentive Dosage Form (GRDF) or Immediate-Release (IR) Tablet to Healthy Volunteers ($N=14$)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>GRDF</th>
<th>IR Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{max}$ (mg/h)</td>
<td>3.3 ± 0.3*</td>
<td>4.8 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>$t_{max}$ (h)</td>
<td>4.3 ± 0.5*</td>
<td>1.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>$A_{0-5.1}$ (mg)</td>
<td>7.2 ± 1.1*</td>
<td>13.0 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>$A_{0-24.1}$ (mg)</td>
<td>17.0 ± 3.4</td>
<td>17.7 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>6.5 ± 1.4*</td>
<td>4.1 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{max}$ (mL/h)</td>
<td>642 ± 86*</td>
<td>432 ± 12</td>
<td></td>
</tr>
<tr>
<td>$t_{max}$ (h)</td>
<td>2.4 ± 0.1*</td>
<td>1.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>$Volume_{0-5.1}$ (mL)</td>
<td>1691 ± 155*</td>
<td>1251 ± 63</td>
<td></td>
</tr>
<tr>
<td>$Volume_{0-24.1}$ (mL)</td>
<td>3169 ± 221*</td>
<td>2281 ± 77</td>
<td></td>
</tr>
<tr>
<td>Efficiency$_{0-5.1}$ (mL/mg)</td>
<td>291 ± 33*</td>
<td>127 ± 18</td>
<td></td>
</tr>
<tr>
<td>Efficiency$_{0-24.1}$ (mL/mg)</td>
<td>213 ± 30</td>
<td>163 ± 20</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{max}$ (mmol/h)</td>
<td>67.6 ± 8.7</td>
<td>56.2 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>$t_{max}$ (h)</td>
<td>3.0 ± 0.6*</td>
<td>1.8 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>$A_{0-5.1}$ (mmol)</td>
<td>167 ± 25</td>
<td>150 ± 10</td>
<td></td>
</tr>
<tr>
<td>$A_{0-24.1}$ (mmol)</td>
<td>276 ± 25*</td>
<td>215 ± 13</td>
<td></td>
</tr>
<tr>
<td>Efficiency$_{0-5.1}$ (mmol/mg)</td>
<td>25.9 ± 2.8*</td>
<td>15.2 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Efficiency$_{0-24.1}$ (mmol/mg)</td>
<td>17.5 ± 1.8</td>
<td>15.6 ± 2.1</td>
<td></td>
</tr>
</tbody>
</table>

$V_{max}$: maximal excretion rate; $t_{max}$: time for maximal excretion rate; $A$: amount excreted; MRT: mean residence time. Efficiency = the ratio between the pharmacodynamic measurement and the amount of excreted drug.

*Significantly different from IR tablet, $p < 0.05$.

Figure 1. In vitro release kinetics of 60 mg furosemide into phthalate buffer (pH 4.6) from gastroretentive dosage form (GRDF) or immediate-release (IR) tablet.
DISCUSSION

The outcomes of this study highlight the ability to improve the pharmacodynamic effects of furosemide by continuous and prolonged input of the drug to the stomach and the upper part of the intestine using a new GRDF technology. It has been proposed that furosemide activity is dependent on (1) electrolyte and volume status of the body, 25-27 (2) dosage, 28 and (3) rate of administration, 5,20 which affects the time course of the drug input to the site of action. 29 Specifically, it has been shown that a slow and constant mode of furosemide administration may be associated with elevated efficiency. 30,31 This phenomenon of non-concentration-dependent pharmacodynamics was also demonstrated by the similar magnitude of the diuretic effect despite significant differences in furosemide bioavailability when administered as intravenous bolus, IR tablet, 32 or controlled-release tablet. 9-11

This mode of the administration-dependent effect is explained by the “efficiency concept” 29,31,32 that occurs due to progressive saturation of the “response system,” caused by confined availability of the drug molecules to the receptor, which leads to a diminishing pharmacodynamic response compared to the drug concentration. This concept was proposed for furosemide actions, both in patients and healthy volunteers, and was shown to be valid also for various types of pharmacological activities, including the action of antineoplastic drugs, opioids, and antibacterials. 33

We developed a furosemide GRDF that is retained in the stomach as a result of the polymeric platform. The gastroretentivity of this unfolding expandable dosage form is contributed by the combination of the extended dimensions (5.5 × 2.1 cm) together with considerable rigidity that is provided by the polymeric strips in the platform’s frame. 15,17 We have found that this combination provides synergistic gastroretentive properties and thus extends the duration of sustained release in the stomach. Other approaches to design GRDFs include swelling, floating, or mucoadhesive dosage forms. However, all of these pharmaceutical approaches yielded suboptimal retention in the human stomach. 34

To ascertain the gastroretentivity of the novel furosemide-GRDF, an X-ray was taken 5 hours postadministration. The X-ray revealed that in 64% of the volunteers, the GRDF was retained in the stomach for at least 5 hours. These data are in accordance with our earlier studies, which evaluated the retentivity of drug-free GRDFs. On the basis of the results of current and previous studies, we may assume that extended gastric retention of 3 hours was achieved in almost all of the volunteers. 17

Overall sodium excretion is the primary cause for clinical use of loop diuretics. 26 However, a major clinical problem related to these drugs is “postdiuretic overshoot” due to the retrieval of salt by the nephrons once the diuretic effect has worn off, which might completely nullify the sodium depletion over a 24-hour period. 6,7 In this sense, it is important to note that the furosemide-GRDF hereby described showed enhanced magnitude of drug effects when compared to the standard IR treatment, which is in accord with the clinical need. An additional advantage of the furosemide-

Figure 2. Kinetics of furosemide urinary excretion rate (a) or duration of furosemide absorption (b) following administration of 60 mg furosemide as gastroretentive dosage form (GRDF) or immediate-release (IR) tablet to healthy volunteers (N = 14). In panel (a), the data points are the mean observed pharmacokinetic data, and the solid lines are the best fits according to the pharmacokinetic model. In panel (b), the data points were calculated according to Wagner-Nelson method, and the solid lines are the best fits according to the sigmoid model.
GRDF is that a certain extent of natriuresis may be accompanied by more extensive diuresis (Figure 6).

As can be seen from Figures 3 and 4, the slow input of furosemide from the GRDF minimized the counteractivity of the body for the first 3 to 4 hours after the administration and delayed the activation of the compensatory mechanisms. Then, an acute tolerance emerged as a steep decline in the diuretic and natriuretic effects, and the magnitude of response thereafter was similar to the response obtained following the IR tablet. Due to temporal differences in the activation of tolerance mechanisms between the studied dosage forms, despite the lower furosemide excretion rate for GRDF during the first 5 hours postadministration, the GRDF was characterized by higher diuretic and natriuretic efficiencies, leading to higher amounts of urine and sodium excreted (see Table II).

We studied the pharmacokinetic-pharmacodynamic relationship of furosemide and the mechanism of tolerance development in our experimental settings by means of a pharmacokinetic-pharmacodynamic modeling approach. In contrast to the previous reports that applied the indirect relationship between the furosemide excretion rate and the pharmacodynamic outcomes, our experimental data suggest a direct pharmacokinetic-pharmacodynamic relationship for furosemide. This finding may be related to differences in the applied dosage forms (oral GRDF and IR tablets in our studies as opposed to single or multiple intravenous infusions) and/or the experimental settings (water replacement, food intake, and the sampling times) between the studies.

To describe the tolerance development in our study, we suggested that the drug effect is due to two mechanisms that contribute to the diuretic action: one is affected and the other is not influenced by tolerance development. The rationale for such a model is the observed hysteresis (see Figure 4), in which the concentration-effect profile for the slow input (GRDF) is steep for the first 5 hours and diminishes dramatically thereafter until it becomes identical to the pharmacodynamic slope that describes the response to the fast (IR) input.

To describe the time course of tolerance development, we applied a feedback mechanism using an endogenous modifier. This term represents a hybrid of all the antagonistic activities that are activated by the diuretic/natriuretic effects of the drug in an attempt to maintain homeostasis. We assumed that the concentrations of the modifier increase in a linear fashion if the furosemide excretion rate exceeds a certain critical value. Since in our study, the tolerance did not dissipate toward the end of the sampling period, a decrease in modifier concentrations could not be assessed from the observed data and was not introduced in the pharmacokinetic-pharmacodynamic model.
Tolerance phenomenon for furosemide was reported before in both animals and humans. It was related to acute hypovolemia associated with rapid diuresis, which activates compensatory homeostatic mechanisms, leading to increased proximal and distal tubular reabsorption in an effort to preserve an extracellular volume. While the exact mechanism by which tolerance occurs is unclear, these compensatory changes were attributed to a combination of the following: a triggering of the sympathetic and the renin-angiotensin-aldosterone systems, a decrease in atrial natriuretic peptide levels, an increase in vasopressin levels, and local renal hemodynamic processes.

Diuretics such as furosemide are known to inhibit the Na\(^+\)-K\(^+\)-2Cl\(^-\) symporter from the luminal side of the medullary and cortical parts of the thick ascending limb of the loop of Henle by a competitive binding with the chloride ion. This leads to an increase in electrolyte...
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excretion, which is accompanied by enhanced tubular flow and volume of urine excreted. However, the kinetics of the natriuretic effect and the diuretic effect are not necessarily parallel, as shown in this investigation (see Figure 6) for the studied modes of administration and elsewhere. It was shown that natriuresis is influenced only to a limited extent by water replacement or total liquid loss. This is because the patterns of kidney response for diuresis and natriuresis are at least partially autonomous, based on the fact that the homeostatic mechanism for body sodium content operates independently, although in harmony, with the homeostatic mechanism for the water content.

As previously described, furosemide pharmacodynamic response is associated with considerable intersubject variability, as illustrated in Table I. However, for most of the individual subjects, the data followed the same trend of higher diuresis and natriuresis following GRDF administration in comparison to the IR dosage form. Thus, the average diuretic and natriuretic responses for the studied dosage forms aptly represent the observed individual data trends.

Different subjects receiving the same or various dosage forms can have identical bioavailability with substantially different overall pharmacodynamic effects, as occurred in the present study (see Figure 5). This phenomenon, as well as the complex pharmacokinetic-pharmacodynamic correlation described here and earlier, illustrates the prudence that has to be taken when developing controlled-release dosage forms, including GRDFs, based on pharmacokinetic data alone.

The furosemide-GRDF applied in this study may be further optimized by virtue of more sustained release of the drug. This may further delay the activation of compensatory responses and improve furosemide treatment by yielding a diuretic response for a prolonged time period and augmentation of drug efficiency.

Our non-drug-specific GRDF was hitherto evaluated in dogs as a drug carrier for riboflavin and levodopa and yielded an extended absorption phase when compared to nongastroretentive controlled-release dosage forms. These accumulating findings substantiate the concept that the gastroretentivity provided by the novel GRDF may become a practical approach for advancing therapy with narrow absorption window drugs.

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