Formulation of Convenient, Easily Scalable, and Efficient Granisetron HCl Intranasal Droppable Gels

Howida K. Ibrahim, Nevine S. Abdel Malak, and Sally A. Abdel Halim

ABSTRACT: Deacetylated gellan gum and two sodium alginate polymer types were used each at three concentrations in the suitable range for their sol-gel transition. The prepared nine droppable gels were evaluated in vitro, ex vivo through sheep nasal mucosa, as well as in vivo in comparison to drug solution given intravenously and orally at the same dose. The prepared formulas gelled instantaneously in simulated nasal fluid and the obtained gels sustained their shear thinning and thixotropic behavior up to 48 h. Polymer type and concentration had significant effects on the apparent viscosities and the in vitro release profile of granisetron from the prepared gels. The drug release data best fitted a modified Higuchi equation with initial burst and followed Fickian diffusion mechanism. A 0.5% gellan-gum-based formula sustained the in vitro drug release up to 3 h and enhanced the drug permeation without need for an enhancer. The histopathological study revealed the safety of the tested formula. Intranasal delivery recorded double the drug bioavailability in comparison to the oral route. It had an absolute bioavailability of 0.6539 and the maximum plasma drug concentration reached after 1.5 h. The developed formula could be promising for the management of chemotherapy-induced nausea and vomiting regarding its improved bioavailability, patient acceptability, and ease of production.

Keywords: granisetron HCl, droppable gel, intranasal delivery

INTRODUCTION

Nausea and vomiting are the most upsetting adverse reactions of cancer chemotherapy. Serotonin (5-hydroxytryptamine, 5-HT) was proved to be at least partially responsible for producing those effects. Ligand binding to 5-HT3 receptor type induces nausea and vomiting. Thus, current guidelines propose 5-HT3 receptor blockage as an intervention. Highly potent and selective 5-HT3 receptor antagonists include ondansetron, granisetron, and tropisetron. Granisetron is the most selective with consequent less adverse effects. It prevents acute emesis by acting at both peripheral (GI tract) and central (medullary chemoreceptor zone) sites. Granisetron proved to be effective and well tolerated as antiemetic in children too. Orally administered granisetron is subjected to hepatic first pass effect. Granisetron HCl is available commercially as oral tablets as well as a solution for iv administration. Some trials were conducted for the transdermal delivery of granisetron to overcome the hepatic first pass metabolism. A study investigated delivering it as suppository and another through the buccal cavity. Clinical trials in animals and healthy volunteers proved the possibility of delivering granisetron HCl solution through the nasal mucosa with rapid absorption and improved bioavailability in comparison to oral administration. The drug had an excellent safety profile regarding irritation to the nasal mucosa and abnormal changes in clinical laboratory tests. Literature lacks formulation trials of granisetron HCl for the intranasal delivery except for the preparation of freeze-dried microparticles composed of granisetron–cyclodextrin complex and carboxymethylcellulose. This work focused on the solubilization of granisetron base and did not test the drug bioavailability.

Intranasal delivery is a convenient alternative to the parenteral route. The high blood supply and permeability of the nasal mucosa guarantee systemic drug delivery. Yet, mucociliary clearance limits the residence time for drug to be absorbed. Droppable gels improve nasal drug absorption. Gellan gum and alginates are biodegradable and nontoxic polysaccharides. Their high water holding capacity and mucoadhesive potential make them useful carriers for the nasal cavity without harmful effects. Thus, the aim of this work was to formulate granisetron HCl as intranasal droppable gels for improved patient compliance and enhanced therapeutic effect. The work will investigate different ion activated in situ gelling polymers at different concentrations with and without permeation enhancer. Thorough in vitro and ex vivo evaluations will be conducted and the formula of choice will be compared to drug solution given orally and intravenously in experimental animals.

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Table 1. Composition and Evaluation of the Prepared Granisetron HCl Droppable Gels

<table>
<thead>
<tr>
<th>formula</th>
<th>polymer type</th>
<th>polymer concentration (%)</th>
<th>RE&lt;sub&gt;0&lt;/sub&gt; (%)</th>
<th>Farrow’s constant (N)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mean ± SD</td>
<td>Tukey confidence limits</td>
</tr>
<tr>
<td>F1</td>
<td>Low molecular weight alginate</td>
<td>0.5</td>
<td>97.89 ± 0.4336</td>
<td>(96.619–98.774)</td>
</tr>
<tr>
<td>F2</td>
<td>0.75</td>
<td></td>
<td>94.59 ± 0.2627</td>
<td>(93.844–95.149)</td>
</tr>
<tr>
<td>F3</td>
<td>1</td>
<td></td>
<td>92.69 ± 0.3508</td>
<td>(91.792–93.535)</td>
</tr>
<tr>
<td>F4</td>
<td>High molecular weight alginate</td>
<td>0.5</td>
<td>93.62 ± 0.3002</td>
<td>(92.861–94.353)</td>
</tr>
<tr>
<td>F5</td>
<td>0.75</td>
<td></td>
<td>90.46 ± 0.3020</td>
<td>(89.670–91.170)</td>
</tr>
<tr>
<td>F6</td>
<td>1</td>
<td></td>
<td>85.35 ± 0.3500</td>
<td>(84.480–86.220)</td>
</tr>
<tr>
<td>F7</td>
<td>Deacetylated gellan gum</td>
<td>0.1</td>
<td>99.31 ± 0.2524</td>
<td>(98.643–99.897)</td>
</tr>
<tr>
<td>F8</td>
<td>0.2</td>
<td></td>
<td>96.90 ± 0.3464</td>
<td>(95.839–97.561)</td>
</tr>
<tr>
<td>F9</td>
<td>0.5</td>
<td></td>
<td>70.53 ± 0.2503</td>
<td>(69.922–71.165)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Granisetron HCl is added as 1% in all formulas. <sup>b</sup>Farrow’s constant is calculated from the exponential formula (F<sup>0</sup> = η·G).

### METHODS

#### Materials

Granisetron HCl was kindly gifted by Amoun Pharmaceutilcs, Egypt, two types of sodium alginate; low and high molecular weights (LMW, HMW), deacetylated gellan gum, and acetonitrile (HPLC grade) were purchased from Sigma-Aldrich, St. Louis, MO, U.S.A., sodium chloride, potassium chloride, and calcium chloride dihydrate (ADWIC Co., Egypt). The simulated nasal fluid was composed of 7.45 mg/mL NaCl, 1.29 mg/mL KCl, and 0.32 mg/mL CaCl<sub>2</sub>·2H<sub>2</sub>O and was pH adjusted at 5.5.

#### Stability of Granisetron HCl in Nasal Mucosa Extract

Fresh excised nasal sheep mucosa was extracted in normal saline by stirring for 5 h. Granisetron was added to 5 mL of the collected extract and kept for 24 h at 37 °C. The remaining drug content was analyzed using the stability indicating HPLC assay developed by Souri et al.<sup>21</sup> A 75:25 v/v mixture of saline and acetonitrile and 25 mM KH<sub>2</sub>PO<sub>4</sub> was used as the mobile phase. Separation was done using a Nova-Pak C<sub>8</sub> column (60 Å, 4 μm, 3.9 mm × 150 mm, Waters) and detection was performed at 200 nm. A paired <i>t</i>-test was conducted to evaluate the results.

#### Preparation of Droppable Gels

The used polymer concentration ranges were determined based on literature<sup>22,23</sup> as well as on preliminary experiments. The three polymers were tested in concentrations ranging from 0.05 to 2%. Three concentrations were selected for each polymer. Sols at the selected concentrations should have spontaneous sol-gel transformation and all are less than the concentration leading to a gel without the addition of the nasal fluid. Deacetylated gellan gum sols were prepared in ultrapure water with stirring at 90 °C at three concentrations (0.1, 0.2, and 0.5%). The drug was dissolved in the resulting sols after cooling to room temperature as 1% w/v. Alginate sols were prepared by sprinkling the corresponding amounts of either the low or high molecular weight grades in ultrapure water. The sols were left overnight at room temperature and the drug was added by stirring. The alginate sols were prepared at three concentrations, namely, 0.5, 0.75, and 1%. The composition of the prepared formulas is shown in Table 1.

#### Gelling and Rheological Properties

Sol-gel transition of the prepared droppable gels was tested visually in simulated nasal fluid. Gellation was tested by mixing at 1:1 formula to nasal fluid ratio, as well as, by dropping the formulas onto the nasal fluid and vice versa. The obtained gels were kept and observed for 48 h postmixing.

The rheological properties of the drug loaded formulas were determined using a cone and plate Brookfielld viscometer (model HBDV-I, Brookfield Engineering Laboratories, Inc., Middleboro, MA, U.S.A.) at 25 °C using 1 mL sample aliquots. Apparent viscosity values were measured at different angular velocities (10–100 rpm) with a similar wait before each change in speed. Rheograms were constructed by plotting apparent viscosity values versus angular velocities from 10 to 100 and down back. Measurements were done in duplicate. For comparison, the exponential formula was used and the exponent N (Farrow’s constant) was calculated.

#### In Vitro Release Profile

One gram of droppable gel samples were filled in dialysis bag (Spectrapor membrane tubing No. 2 Spectrum Medical Industries, U.S.A.) and mounted in a 100 mL simulated nasal fluid. The test was carried out in United States Pharmacopia XXVIII dissolution apparatus Type II operated at 50 rpm and 37 ± 1 °C. Aliquots of 1 mL in volume were withdrawn up to 3 h. The drug content was determined spectrophotometrically after proper dilution.

The release efficiency after 3 h (RE<sub>0</sub>) was measured according to Modi and Tayade<sup>24</sup> as a parameter for the release extent. ANOVA analysis with subsequent Tukey–Kramer multiple comparison test were conducted to study the effect of both polymer type and polymer concentration on the release behavior. The (q) values were calculated and compared to a (q) value from the studentized range distribution. Tukey’s confidence limits were also calculated for all pairwise comparisons.

Mathematical modeling of the release data from the droppable gels was done using DDSolver (an Excel add-in software package; see Table 2). The adjusted coefficient of determination (R<sup>2</sup> adjusted) was considered for finding the best fit of the release data to the zero order, first order, as well as, Higuchi equation and its modified form describing the initial burst effect and <i>n</i> is Korsmeyer–Peppas exponent.

### Table 2. Mathematical Modeling of the In Vitro Release Data for the Selected Granisetron HCl Droppable Gel Formulaa

<table>
<thead>
<tr>
<th>formula</th>
<th>R&lt;sup&gt;2&lt;/sup&gt; adjusted</th>
<th>Higuchi with &lt;i&gt;F&lt;sub&gt;0&lt;/sub&gt;&lt;/i&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Korsmeyer–Peppas&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3</td>
<td>0.9203</td>
<td>28.455</td>
<td>7.141</td>
</tr>
<tr>
<td>F6</td>
<td>0.9658</td>
<td>22.375</td>
<td>6.402</td>
</tr>
<tr>
<td>F9</td>
<td>0.9773</td>
<td>22.160</td>
<td>5.336</td>
</tr>
</tbody>
</table>

<sup>a</sup>Composition of the formulas is shown in Table 1. <sup>b</sup>Higuchi with <i>F<sub>0</sub></i> model: = <i>F<sub>0</sub></i> + <i>K<sub>H</sub></i><i>t</i>, Korsmeyer–Peppas with <i>F<sub>0</sub></i> model: = <i>K<sub>CP</sub></i><i>F<sub>0</sub></i><i>e</i><i>−</i><i>k<sub>c</sub></i><i>t</i>, where <i>F<sub>0</sub></i> is the cumulative quantity of drug released at time <i>t</i>, <i>F<sub>0</sub></i> is burst effect and <i>n</i> is Korsmeyer–Peppas exponent.
burst release effect ($K_p$). The nontransformed release data were also fitted to the Korsmeyer–Peppas model and its modified form with burst25 employing Nelder–Mead simplex algorithm. The exponent $n$ values were calculated using the nonlinear least-squares curve-fitting technique and were used for investigating release mechanism.26

Ex Vivo Permeation and Local Toxicity on Sheep Nasal Mucosa. The permeation of the selected droppable gels was assessed through freshly excised sheep nasal mucosa. Hydroxypropyl β-cyclodextrin (10%) was added as an enhancer, composition of the tested formulas is shown in Table 3. The test was conducted in a modified diffusion cell with a diffusional area of 3.14 cm$^2$ and a 7 mL receiver chamber capacity. The droppable gels were added to the donor compartment after mixing with nasal fluid at 1:1 ratio. The permeated drug was received in simulated nasal fluid maintained at 37 °C and magnetically stirred at 50 rpm. The whole receptor fluid was replaced at each time interval and analyzed by HPLC. The mean cumulative amount permeated per unit surface area of the nasal mucosa was plotted versus time. The slope of the linear portion of the plot was calculated to represent the steady state flux ($J_s$). Apparent permeability coefficient ($K_p$) was calculated by dividing the flux by initial concentration of the drug in the donor compartment.

Permeation data was subjected to statistical analysis using one way ANOVA and Tukey multiple comparison tests. The effect of the enhancer on the permeation profiles for both formulas was evaluated using the similarity factor.$^{29}$

At the end of the permeation test, the used nasal mucosa sections were transferred into 10% formalin solution. They were stained with hematoxylin–eosin and examined under the light microscope (Axiovert 200MAT, Carl Zeiss, Germany) by a pathologist. A control nasal mucosa section was also examined after soaking in nasal fluid for 7 h.

In Vivo Evaluation. The pharmacokinetics of granisetron HCl was studied after the administration of a single intranasal dose (1 mg/kg) of the selected droppable gel formula (F9) to six New Zealand albino rabbits (2.94 ± 0.13 kg). The marketed iv granisetron HCl solution (Emex, Amoun Pharmaceutical Company) was used as the reference, both intravenously and orally at the same intranasal dose in a crossover design. Blood samples were collected from the marginal ear vein at 5, 20, 40 min and 1, 1.5, 2, 3, 4, 5, 6, and 7 h after drug administration.

After centrifugation, the plasma was separated and frozen until analysis. Granisetron HCl was measured in plasma applying the previously described HPLC method with slight modifications.21 The rabbits were fasted overnight with free access to water prior to and during the experiment. The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Pharmacy, Cairo University.

The maximum observed plasma concentration ($C_{max}$) and the time taken to achieve it ($T_{max}$) were obtained directly from the curves. The area under the plasma concentration–time curve up to the last quantified sample (AUC$_{0–\infty}$) was calculated using the trapezoidal rule. The first order terminal elimination rate constant ($k_e$) was estimated by linear regression from the points describing the elimination phase on a log–linear plot. It was used to calculate the AUC$_{0–\infty}$ and $t_{1/2}$. The AUC$_{0–\infty}$ values obtained from the granisetron HCl curves after the administration of the iv and oral solutions as well as the nasal droppable gel were used to calculate the absolute bioavailability.

The mean pharmacokinetic parameter values were compared using a one-way ANOVA followed by Tukey–Kramer multiple comparison test. A p-value of less than 0.05 was considered significant.

Table 3. Ex Vivo Permeation Characteristics of Granisetron HCl through Sheep Nasal Mucosa

<table>
<thead>
<tr>
<th>tested formulas</th>
<th>$J_s$ (μg·cm$^{-2}$·h$^{-1}$)</th>
<th>$K_p$ (cm·h$^{-1}$) × 10$^{-3}$</th>
<th>mean ± SD</th>
<th>Tukey confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>208.65 ± 5.09</td>
<td>69.55 ± 3.01</td>
<td>(62.369–77.331)</td>
<td></td>
</tr>
<tr>
<td>F6 + enhancer$^b$</td>
<td>236.50 ± 3.50</td>
<td>78.83 ± 3.58</td>
<td>(69.041–86.845)</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>444.67 ± 5.01</td>
<td>148.22 ± 3.52</td>
<td>(138.98–156.50)</td>
<td></td>
</tr>
<tr>
<td>F9 + enhancer$^b$</td>
<td>432.94 ± 5.50</td>
<td>144.15 ± 3.51</td>
<td>(135.67–153.09)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Composition of the formulas is shown in Table 1. $^b$Enhancer is 10% hydroxypropyl β-cyclodextrin. $^c$Permeation coefficient, $K_p = J_s/C_o$, $C_o = 300$ μg/mL.

Figure 1. Rheological properties of (a) LMW alginate, (b) HMW alginate, and (c) gellan gum droppable gels before and after gelation in simulated nasal fluid.
RESULTS AND DISCUSSION

Stability of Granisetron HCl in Nasal Mucosa Extract. The remaining granisetron HCl amount after 24 h in nasal mucosa extract was 98.54%. It was nonsignificantly different from the initial added amount (99.21%) indicating high drug stability.

Preparation of Droppable Gels. Gellan gum and alginate have been granted regulatory approvals as pharmaceutical excipients and food additives, and literature thoroughly investigated their safety for intranasal administration.

Gelling and Rheological Properties. Sol-gel transition occurred immediately upon contact with the simulated nasal fluid regardless of the mixing ratio or order (lag time values were less than 10 s). This rapid gelation is essential to overcome the mucociliary clearance from the nasal cavity. Mucus transit time ranges from 15 to 20 min with a transport rate of 5 mm/min.

All the prepared formulas exhibited shear thinning behavior before gelation (N > 1, Table 1). Polymer type had a significant effect on the rheological properties. High molecular weight alginate-based systems recorded comparable viscosity values to gellan gum ones, Figure 1b and c. On the other hand, the viscosities and degrees of pseudoplasticity of low molecular weight alginate based formulas were markedly lower. Their upward and downward curves were almost superimposed showing no thixotropic behavior, Figure 1a. Increasing polymer concentration markedly increased apparent viscosity and degree of pseudoplasticity. Thixotropy was prominent only for formulas F5, F6, and F9, prepared at the highest concentrations of HMW alginate and gellan gum polymers. Thixotropy will add an advantage to gel−sol-gel behavior during use (e.g., spraying or dropping of the sols) and can ensure the formation of a firm reservoir in the nasal mucosa.

Viscosity increased significantly after gelation. Similarly, did the pseudoplastic and thixotropy degrees. The rheograms of LMW alginate based formulas had very low apparent viscosities and degrees of pseudoplasticity even in the presence of nasal fluid ions. The obtained rheograms after sol-gel transition were stable for more than 48 h for the three polymers, data are not shown.

In Vitro Release Profile. Figure 2a, b, and c shows the in vitro release profile of granisetron from the prepared droppable gels, whereas the calculated RE3h values are listed in Table 1. The calculated (q) values were larger than the

Figure 2. In vitro release profiles of granisetron from (a) LMW alginate, (b) HMW alginate, and (c) gellan gum droppable gels in simulated nasal fluid (n = 3; error bars indicate SD).

Figure 3. Ex vivo permeation of granisetron HCl as a function of time from the selected droppable gels with and without enhancer through sheep nasal mucosa (n = 3).

Figure 4. Histopathological sections of (a) untreated, (b) alginate gel treated, (c) gellan gum treated, and (d) gellan gum/enhancer treated nasal mucosa at magnification of 100x. Granisetron is loaded in gels as 1% w/v and treatment lasted for 7 h.
The release rate and extent can be increased by increasing the polymer concentration, as Poly (4-5-6-7) showed the highest release rate and extent. This could be rationalized in terms of increasing polymer concentration significantly affecting the drug release from the prepared droppable gels. The polymers can be arranged in an ascending order according to their ability to sustain granisetron release as LMW alginate < HMW alginate < gellan gum. Low molecular weight alginate based formulas released 100% of their loaded drug within 30 min. The low viscosity could be the cause for this poor drug release sustainment. This duration was longer for HMW alginate based formulas (120–240 min). Only 0.5% gellan gum formula succeeded in controlling the drug release up to 360 min.

Increasing polymer concentration significantly decreased the release rate and extent. This could be rationalized in terms of the marked increase in viscosity at higher polymer concentrations.

The data of droppable gel formula F3, F6, and F9 (showing controlled drug release) were fitted into different kinetic models. The highest $R^2_{\text{adjusted}}$ values were obtained with modified Higuchi equation describing the initial burst release effect. The outputted burst and $T_{90\%}$ values are shown in Table 2. The release data better fitted the Korsmeyer–Peppas model rather than its modified form with burst. The ($n$) exponent values ranged from 0.306 to 0.341 supporting the diffusion mechanism, Table 2. The drug release is controlled by diffusion through the three-dimensional structures of gellan gum and alginate after sol-gel transition. In the presence of cations, gellan gum chains bind forming double-helical junction zones, which further aggregate in the presence of water giving 3-D networks. Sodium alginate forms 3-D ionotropic hydrogel matrices through the interaction of its guluronic acid moieties with calcium ions.

Formulas F6 and F9 recorded significantly lower burst and higher $T_{90\%}$ values than those of F3 and were selected for further investigations.

### Ex Vivo Permeation and Local Toxicity on Sheep Nasal Mucosa
Sheep nasal mucosa was selected because of its human-like histology. Gellan gum based formula (F9) recorded significantly higher flux than that of alginate formula (F6), Figure 3 and Table 3. Hydroxypropyl $\beta$-cyclodextrin showed no permeation enhancing effects of granisetron HCl from both formulas. The calculated similarity factors were 98.85 and 97.32 for formulas F6 and F9 with and without enhancers, respectively. The polar nature and the low molecular weight of the drug (348.9 Da) suggest crossing the nasal epithelial membrane by paracellular route.

Figure 4a–d shows that the structure of the mucosa was well preserved after 7 h exposure to the drug loaded gels with and without enhancer. No signs of irritation or toxicity were detected. Histological sections of the control and the treated nasal mucosa were similar in tissue architecture.

### In Vivo Evaluation
Figure 5 shows the plasma drug concentration versus time curves after nasal, oral, and iv administration of the droppable gel formula F9 in comparison to the oral and iv solutions (references) to experimental animals. The error bars represent ±SD.

### Table 4. Mean Pharmacokinetic Parameters of Granisetron HCl after Intranasal Administration of the Droppable Gel Formula F9 in Comparison to the Oral and Iv Solutions

<table>
<thead>
<tr>
<th>parameter</th>
<th>intranasal droppable gel</th>
<th>oral solution</th>
<th>iv solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
<td>19.38 ± 2.56</td>
<td>13.158 ± 3.23</td>
<td>31.345 ± 2.18</td>
</tr>
<tr>
<td>AUC$_{0-7}$ (g.h/ml)</td>
<td>3416.155 ± 11.38</td>
<td>1935.727 ± 13.17</td>
<td>4718.699 ± 12.40</td>
</tr>
<tr>
<td>AUC$_{0-12}$ (g.h/ml)</td>
<td>3611.731 ± 14.12</td>
<td>1988.508 ± 9.56</td>
<td>5523.708 ± 15.09</td>
</tr>
<tr>
<td>AUC$<em>{0-\infty}$/AUC$</em>{0-\infty}$</td>
<td>0.946</td>
<td>0.973</td>
<td>0.854</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>90 ± 5.52</td>
<td>150 ± 7.34</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>85.56 ± 4.18</td>
<td>57.27 ± 0.12</td>
<td>150.65 ± 0.04</td>
</tr>
<tr>
<td>absolute bioavailability$^d$</td>
<td>65.39%</td>
<td>35.99%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Test. $^b$References. $^d$All values are mean ± SD, n = 6. $^d$Absolute bioavailability = (AUC$_{0-\infty}$/AUC$_{0-\infty}$test)/(AUC$_{0-\infty}$/AUC$_{0-\infty}$reference)
administration of granisetron. The calculated pharmacokinetic parameters are shown in Table 4. Intranasal administration of granisetron HCl significantly improved the drug absorption rate and extent compared to the oral route. This is due to escaping the hepatic first pass metabolism. Formulating the drug as a droppable gel via the nasal route significantly increased its $t_\text{max}$ in body compared to the oral solution. This could be due to the longer residence time in the nasal cavity and the prolonged in vitro release profile of the drug from the gels. The maximum plasma concentrations were reached after 1.5 and 2.5 h for intranasal and oral routes, respectively. Blum et al.\textsuperscript{33} reported that the time to reach peak concentration was 3 h after administration of oral tablets in "healthy individuals; PDR, 2005". The intranasal droppable gel recorded an absolute relative bioavailability of 0.6539. Its measured $C_{\text{max}}$, AUC$_{0-7}$, and AUC$_{0-\text{inf}}$ were significantly lower than the corresponding parameters after iv administration of the drug solution. On the other hand, Jong Soo Woo\textsuperscript{16} reported that the bioavailability of granisetron solution following nasal administration was comparable to that following iv administration of the same dose in rats, regarding their $C_{\text{max}}$ and elimination half-life. This could be justified in terms of the different drug dosage forms.

\section*{CONCLUSION}

Granisetron HCl was successfully formulated as a droppable gel for intranasal administration. The drug was stable and did not show histological evidence of irritation or toxicity. Droppable gels combine the advantages of accurate dosing and easy administration of solutions and the longer contact time and prolonged release profile of gels. The release profile was tailored by changing the polymer type and concentration. Intranasal administration doubled the granisetron bioavailability in comparison to the oral route. It is more convenient and easier to administer in relation to the iv injection. The maximum drug concentration in plasma reached after 1.5 h, which suggests dosing 1 h before radiation therapy.

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\section*{Notes}

The authors declare no competing financial interest.

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