Companion animal physiology and dosage form performance

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Received 2 May 2003; accepted 18 February 2004

Abstract

Among the most critical parameters for any drug candidate are tolerability, dose, solubility and permeability. For controlled release formulations, gastrointestinal transit is an added hurdle. While we might assume that intestinal transit is independent of the drug candidate, the relative importance of gastrointestinal transit time (GITT) depends directly on the other parameters. For example, a formulation of a drug with low solubility (LS) and/or low permeability (LP) characteristics might provide the required systemic concentrations when administered with food, but not if administered on an empty stomach. In the LS case, the drug may require the solubilizing effects of increased fluid and bile salts that accompany the meal. Likewise, a controlled release formulation of a drug with a region of preferred absorption may empty from the fasted stomach and move beyond the region before drug release is complete. Companion animals (e.g. cats and dogs) differ from humans and each other with respect to GITT, food effects, eating habit influences, breed and size variability, gastric pH, intestinal enzymes, GI permeability and absorption regions. This review examines how the anatomy and physiology of companion animals relates to the performance of orally administered immediate and controlled release formulations. Examples are presented of techniques used to predict the dose and acceptable solubility of drug candidates, and the performance of formulations in companion animals.

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Keywords: Controlled release; Gastrointestinal transit; IVIVC; Dog; Cat

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1. Gastrointestinal physiology

As described in Stevens’ Comparative Physiology of the Vertebrate Digestive System [1], the gastrointestinal tract of the carnivores (dog and cat) are short and relatively simple (Fig. 1), and while the absolute volumes of the stomach, small and large intestines are larger for the dog, the relative volumes of the stomach and large intestines are similar (Table 1). The relative size of the cat small intestine is shorter than that of the dog. The ileum represents a smaller contribution to the small intestine in these animals than in humans. In these animals, there is also a small cecum (smallest in the cat) and an unsacculated colon. The dog large intestine anatomy reflects the human in at least one aspect: it is comprised of ascending, transverse and descending regions (Fig. 2).

The stomach is both a reservoir and a mixing/grinding organ. Detailed reviews of the stomach physiology can be found in Johnsons’ Physiology of the Gastrointestinal Tract [2]. Brown et al. described the grinding function of the stomach as a requirement for breaking down food particles into an echogenic paste—which could then be squeezed out of the stomach through the muscular pylorus [3].

The migrating motility (or myo-electric) complex (MMC), or the “housekeeper wave”, is a periodic gastrointestinal muscle contraction migration that begins in the stomach and duodenum and terminates in the ileum. It is characterized by a period of intense muscular activity following a period of relative quiescence. In the fasting dog, the mean periods of these cycles ranged from 90 to 134 min. As one wave terminated in the distal ileum, another wave would just begin in the stomach/duodenum [4].
2. Permeability: human and animal intubation studies

2.1. Small intestinal permeability

The small intestinal permeability of large molecular weight markers is greater in cats than in dogs. Johnston et al. completed a comprehensive study of the small intestinal permeability in cats, and compared their results with those in humans and dogs [5]. The following probes (in order of decreasing intestinal permeability) were administered: 3-O-Methyl-D-glucose, D-Xylose, L-Rhamnose, 51Cr-EDTA and lactulose. The permeability for the least permeable probes 51Cr-EDTA and lactulose was greatest for cats, then dogs, and smallest for humans (Table 6). There is some evidence for generally better drug permeability in dogs than in humans [6].

2.2. Large intestinal permeability

Large intestinal permeability must be adequate for a candidate to be considered for CR formulation development. Could the permeability of drugs in the dog colon be predicted from human data? Colonic absorption was compared for ten compounds evaluated both in humans and dogs [7]. Delivery of the compounds in the human studies was via a nasogastric tube terminated at the ileal–cesal junction or ascending colon. The compounds were administered to dogs via a colonoscope terminating at the splenic-flexure. Thus while in humans, the entire large intestine was exposed to the drugs, only the descending colon was exposed in the dogs. The exposure of the compounds administered to the colon of each species was compared to the exposure following oral administration (relative bioavailability, RBA). As shown in Fig. 3, the RBA of drugs administered to the dog and human colon were well correlated.

2.3. Conclusions on gastrointestinal physiology and permeability

The cat, with its smaller stomach, is encouraged to eat smaller, frequent meals—the nutrients in which are completely absorbed by the relatively short small intestine. While the small intestine in the cat is shorter than in the dog, the small intestinal transit time (SITT) of small beads was reported as slightly longer in the cat than in the dog [8,9]. The longer SITT and the increased permeability results in more complete absorption of nutrients from the cat’s shorter small intestine.

The dog’s large stomach is ideally suited to receive infrequent large meals. The large amount of nutrients in such meals would require a longer small intestine for complete absorption. The lack of a sacculated colon in these animals probably contributes to this organ’s unusual handling of particles and fluids. In one study, the transit of fluid (Cr-EDTA or PEG-400) and needle-shaped particles (PE tubing, 2 × 2–5 mm)
was determined in dogs (see p. 225 in Ref. [1]). Unlike most other mammals studied (cat was not studied), the particles traversed the colon faster than the fluid marker.

3. Variability of gastrointestinal transit

3.1. Gastric emptying

As shown in Tables 4 and 5, small (1.5–5 mm) diameter beads empty similarly from the stomach of a fasted dog or cat. However, the same beads were retained in the fed cat, but emptied as liquid in the fed dog. It appeared that in the fed state, the cat stomach had a tighter sieve than the dog. This seemed consistent with the findings of Fix et al. [10] that gastric retention was related to breed size. As shown in Fig. 4, the minimum restrictive size for a device retained by the stomach depended on the size of breed within a species, and size of the species. Thus a tetrahedron-shaped device was retained in the 10-kg beagle dog for 24 h, but was rapidly emptied in the 35 kg American foxhound.

The previous discussion emphasized the concern for gastric emptying of monolithic formulations. Ahmed and Kasraian [11] suggested that multiparticulate formulations might be preferred for enteric, delayed or CR delivery in companion animals.

3.1.1. Fasted conditions

While food is likely to have the biggest effect on GITT for these animals, other factors (e.g., surgery and bezores (cats)) may lead to an obstruction or slowing of gastrointestinal transit. Even under the relatively well-controlled conditions of the pharmaceutical kennel (e.g. lighting cycle, controlled temperature, humidity, air exchange, diet, routine exercise, studies, etc.) the fasted beagle showed a wide range in “dosing-to-collection” times of non-disintegrating dosage forms [12]. Four tablets were orally administered to each dog under fasted or fed conditions. The tablets (10 × 6 mm) were administered as a quartet at 0, 2, 4, 6 h, and each was immediately followed with a

Table 2
Small intestine transit time and pH in human, cat and dog

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Region</th>
<th>Human</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transit, fasted</td>
<td>duodenum</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T&lt;sub&gt;50&lt;/sub&gt; or MRT)</td>
<td>jejenum</td>
<td>3–9 (liquid),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(min)</td>
<td>ileum</td>
<td>78 (solid)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>180 ± 60&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≈ 60–111&lt;sup&gt;d&lt;/sup&gt;</td>
<td>144 ± 72</td>
<td></td>
</tr>
<tr>
<td>Transit, fed</td>
<td>duodenum</td>
<td>150–180&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T&lt;sub&gt;50&lt;/sub&gt; or MRT)</td>
<td>jejenum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(min)</td>
<td>ileum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>204 ± 30&lt;sup&gt;g&lt;/sup&gt;</td>
<td>168 ± 84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumenal pH, fed</td>
<td>duodenum</td>
<td>5.5–7&lt;sup&gt;i&lt;/sup&gt;</td>
<td>5–7.6&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>jejenum</td>
<td>5.5–7&lt;sup&gt;i&lt;/sup&gt;</td>
<td>6.2&lt;sup&gt;k&lt;/sup&gt;–7.3&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ileum</td>
<td>7.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.5–7.9&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>general</td>
<td>6&lt;sup&gt;b&lt;/sup&gt;–7&lt;sup&gt;i&lt;/sup&gt;</td>
<td>6.1&lt;sup&gt;n&lt;/sup&gt;–7.6&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumenal pH, fed</td>
<td>duodenum</td>
<td>≈ 5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>5.5–7.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;t&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> [8,9].
<sup>b</sup> gamma scintigraphy: R. Beihn (personal communication).
<sup>c</sup> 2 mm spheres: [36].
<sup>d</sup> [27].
<sup>e</sup> [35].
<sup>f</sup> 30 min after feeding.
<sup>g</sup> [37].
<sup>h</sup> [36].
<sup>i</sup> phase I (90), phase III (78): range (glass bulb-aspiration) [29].
<sup>j</sup> [43].
<sup>k</sup> [39].
<sup>l</sup> [40].
<sup>m</sup> [41].
<sup>n</sup> [42].
<sup>o</sup> [29].
<sup>p</sup> [38].
<sup>q</sup> 1–3 h post (0–15 min pH 4–5, 15–30 min: 5–5.5, 30–45 min: 5.5–6, 45–60 min: >6) [27].
<sup>r</sup> After 50 ml ("fasted") or 150 ml ("fed") [33].

was determined in dogs (see p. 225 in Ref. [1]). Unlike most other mammals studied (cat was not studied), the particles traversed the colon faster than the fluid marker.

3. Variability of gastrointestinal transit

Fig. 3. Correlation of RBA for 11 compounds administered to humans (ICJ) and dogs (DC) [7].
50-ml gavage of water. If the dogs were fasted, they received their regular food rations at 8 h. As shown in Fig. 5, tablets were recovered between 3 and 72 h after dosing. The “dosing-to-collection” time value approximated the GITT. In our experience, it was rare for a dog to defecate during the dark cycle (i.e., at night). This was confirmed by a visual inspection of the cages just prior to the beginning of the light cycle. Therefore, the “dosing-to-collection” time was used interchangeably with GITT. The AMFSD for GITT was: 26.7 ± 12.1 h, with a CV of 45%. Analysis of the frequency histogram revealed a bimodal distribution of GITT (Fig. 6). Tablets that were not recovered soon after the 24-h meal were usually found soon after the 48-h meal. The within-dog variability in GITT was examined in five separate series (Fig. 7). Fig. 7 shows the variability of GITT both between and within dogs. Also Fig. 7 shows the variability in the GITT for individual tablets within the quartet for each dog. For example, dog 34836 showed remarkably reproducible GITT for tablets in each quartet, and across the series. In contrast, dog 35583 exhibited much greater variability within the tablet quartet and across series. The variability did not seem to be particularly sensitive to gender or body weight (within the range studied: 9–14 kg).

### 3.1.2. Fed conditions

The beagle dogs were fed once a day between 10 AM and noon and each received 300–350 g dry dog food (ProLab Canine 1600, PMI Feeds, St. Louis, MO: Crude protein 21%, Crude Fat 8%, Crude Fiber 5.5%, moisture 11%) totaling 1470 kcal. Compared to the fasted condition, the variability in tablet GITT appeared to be slightly less when tablets were administered to fed dogs (AM ± SD: 33.2 ± 12.5 h, CV = 38%) (Fig. 8). The difference between the mean GITT in fed and fasted dogs (~ 6 h) repre-

### Table 3
Composition of the hydrophilic matrix tablet formulations used in the gamma scintigraphic dog studies [19]

<table>
<thead>
<tr>
<th>Item number</th>
<th>Component</th>
<th>% PK (mg/tablet)</th>
<th>% Gamma (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compound A</td>
<td>30</td>
<td>225.0</td>
</tr>
<tr>
<td>2</td>
<td>HPMC&lt;sup&gt;b&lt;/sup&gt;, Methocel K100LV</td>
<td>25</td>
<td>187.5</td>
</tr>
<tr>
<td>3</td>
<td>HPMC&lt;sup&gt;b&lt;/sup&gt;, Methocel K4M</td>
<td>5</td>
<td>37.5</td>
</tr>
<tr>
<td>4</td>
<td>Dicalcium phosphate</td>
<td>39</td>
<td>288.75</td>
</tr>
<tr>
<td>5</td>
<td>Samarium oxide</td>
<td>––</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium stearate</td>
<td>11.25</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>750</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on actual potency of 89.2%.
<sup>b</sup> Methocel<sup>™</sup> grade of HPMC refers to the solution viscosity of a 2% solution in water at 20 °C, i.e., the solution viscosities of Methocel K4M and K100LV are 4000 and 100 cP, respectively.

### Table 4
Gastric emptying of various formulations in the dog and human [26,27]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Parameter</th>
<th>Human</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted, solution</td>
<td>T&lt;sub&gt;50&lt;/sub&gt; (min)</td>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20&lt;sup&gt;e&lt;/sup&gt;, 45&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fasted, 7 × 20 mm&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(h)</td>
<td>1.2 ± 0.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.2 ± 0.4&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bead diameter that emptied with liquids</td>
<td>(mm)</td>
<td>3–7&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.4–4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Volume that initiate fed state&lt;sup&gt;l&lt;/sup&gt;</td>
<td>(ml)</td>
<td>&gt;400&lt;sup&gt;j&lt;/sup&gt;</td>
<td>≈ 150&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fed, time to phase III activity</td>
<td>(h)</td>
<td>2.6–4.8</td>
<td>5.4–13.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> [28].
<sup>b</sup> [33].
<sup>c</sup> range: 30–120 min [34].
<sup>d</sup> diameter of the telemetric pH capsule.
<sup>e</sup> [29].
<sup>f</sup> resulted in a period of stomach muscle quiescence.
<sup>g</sup> [31].
<sup>h</sup> [32].
<sup>i</sup> Range 5–140 min (unpublished observations).
<sup>j</sup> [30].
<sup>k</sup> Gastric emptying after a 50-g snack was 4.6 ± 0.7 h (unpublished observations).

### Table 5
Gastric emptying of various sized beads in the cat [8,9]

<table>
<thead>
<tr>
<th>GET&lt;sup&gt;a&lt;/sup&gt;</th>
<th>State</th>
<th>Human 1.5 mm</th>
<th>5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;50%&lt;/sub&gt; (min)</td>
<td>Fasted</td>
<td>22 ± 13</td>
<td>25 ± 15</td>
</tr>
<tr>
<td>T&lt;sub&gt;90%&lt;/sub&gt; (min)</td>
<td>Fasted</td>
<td>44 ± 7</td>
<td>60 ± 20</td>
</tr>
<tr>
<td>T&lt;sub&gt;50%&lt;/sub&gt; (h)</td>
<td>Fed</td>
<td>6.4 ± 2.6</td>
<td>7.5 ± 4.1</td>
</tr>
<tr>
<td>T&lt;sub&gt;90%&lt;/sub&gt; (h)</td>
<td>Fed</td>
<td>9.1 ± 3.4</td>
<td>9.2 ± 4.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Gastric emptying time.
sented the delay in gastric emptying caused by the meal.

The effect of the tablet order (i.e., the order in which the tablets were administered) on GITT was examined in five fed dogs through three series. This was accomplished by uniquely identifying each non-eroding tablet with an indelible marker. The graphical analysis shown in Fig. 9 can be read as follows: if the bar is divided into four equal segments, then tablet order had no effect on the individual tablet GITT in that dog and series. As shown in Fig. 9, this was the usual case.

3.2. Conclusions on the effects of food on gastric emptying and gastrointestinal transit

The administration of four tablets over six hours in dogs did not seem to have an effect on the individual tablet GITT. Food slightly prolonged the GITT of these tablets. Since 80% of the tablets had GITT > 24 h, CR formulations with extended release durations of < 24 h would nearly always deliver the entire dose in the dog before it was defecated. A delay in gastric emptying—as observed in the fed state—could result in a drug’s increased exposure by a number of mechanisms. While a small dose of a poorly water soluble compound may dissolve in the fasted animal’s gastrointestinal tract, a large dose might not. However, in response to a meal, the increase in secretion rate of fluid and bile salts may be sufficient to dissolve the larger dose. In some cases, the effects of the meal may be a gradual emptying of stomach contents and the drug. This gradual emptying of drug into the small intestine may allow the complete dissolution of the total dose—a little at a time—over several hours.

These mechanisms explain the puzzling effects of food and formulation on the bioavailability of chloramphenicol and mitotane in the cat [13]. In the first case, chloramphenicol tablets gave similar high bioavailability in fed or fasted cats, but the palmitate suspension was not well absorbed in fasted cats. Since chloramphenicol has low water solubility, one explanation is that the suspension emptied from the fasted cat’s stomach so rapidly
Fig. 7. Within dog variability in GITT: fasted beagle dog. Each dog (designated by a number on the “X” axis, female: 0nnn, male: 3nnn) received up to 4 tablets during each “Series” [12].
Fig. 8. Within dog variability in GITT: fed beagle dog. Each dog (designated by a number on the “X” axis; female: 0nnn, male: 3nnn) received up to four tablets during each “Series”: at time 0, 2, 4, 6 h, and then fed normal rations at 8 h [12].
that complete dissolution in the small intestine was not possible. When administered to fed cats, this suspension would be gradually emptied from the stomach, allowing the smaller aliquots of the dose to dissolve and become absorbed. However, the dissolution of the tablets was probably slow—rendering them intact for an extended period of time—resulting in their retention by the small stomach in fasted (and fed) cats.

In the second case, mitotane tablets were not bioavailable in the fasted cat. However, when the tablets were administered with food, good mitotane bioavailability was observed. Apparently the food-induced biliary secretion was sufficient to solubilize mitotane tablets in the fed state. Likewise, there was good exposure from mitotane administered to fasted cats as an oily emulsion. Since mitotane was already dissolved in the oil phase of the emulsion, no additional solubilization (e.g. from bile salts) was needed for absorption to occur.

The effect of meals on drug exposure when the compound exhibits reasonable solubility is more difficult to explain. While the literature has several examples of positive and negative food effect [14,15] only the former will be briefly addressed. When a compound is absorbed in the small intestine but not the large intestine, it is said to have an absorption window. If the formulation moves beyond the absorption window before it disintegrates

![Graph](image-url)

Fig. 9. Effect of tablet administration order on GITT: fed beagle dog. Each dog (designated by a number on the “X” axis) received up to four tablets during each “Series”: at time 0, 2, 4, 6 h, and then fed normal rations at 8 h [12].

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cats (n=6)</th>
<th>Dogs (n=5)</th>
<th>Humans (N=22 or 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>4.89 ± 1.64</td>
<td>1.3 ± 0.6</td>
<td>0.24 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(2.31–6.42)</td>
<td>(0.5–2.9)</td>
<td>DNP*</td>
</tr>
<tr>
<td>L-Rhamose</td>
<td>13.68 ± 5.20</td>
<td>16.8 ± 5.9</td>
<td>10.2 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>(8.4 ± 2.8)</td>
<td>(9.9–24.5)</td>
<td>DNP*</td>
</tr>
<tr>
<td>3-O-Methyl-d-glucose</td>
<td>44.43 ± 18.60</td>
<td>48.9 ± 15.7</td>
<td>56.2 ± 6.5</td>
</tr>
<tr>
<td></td>
<td>(25.3–75.1)</td>
<td>(22.9–75.3)</td>
<td>DNP*</td>
</tr>
<tr>
<td>D-Xylose</td>
<td>31.89 ± 15.78</td>
<td>34.2 ± 11.5</td>
<td>34.0 ± 6.3</td>
</tr>
<tr>
<td></td>
<td>(15.84–58.66)</td>
<td>(15.5–57.8)</td>
<td>DNP*</td>
</tr>
<tr>
<td>51Cr-EDTA</td>
<td>5.96 ± 2.21</td>
<td>DNP*</td>
<td>0.57 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>(2.66–8.93)</td>
<td>DNP*</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD (range) percentage of the orally administered dose recovered in urine obtained 5 h after administration of solutions [5].

* Data not published.
and the drug dissolves, it will be incompletely absorbed. Again, in the fed state, the effects of the meal—gradually emptying the stomach contents of the drug—ensures complete absorption of the dose over several hours.

As was seen in the above cases for slowly dissolving tablets, the food effects on gastric emptying of the dosage form depends on the relative size of the tablet and the species’ pyloric sphincter. In general, monolithic matrix tablets for the extended delivery of compounds exhibiting low solubility and/or low permeability characteristics are more likely to exhibit food effects (Tables 2 and 4).

4. Controlled release formulations in the dog

4.1. Erosion-controlled tablet formulations

CR release can be achieved with tablets (erosion-controlled or non-eroding) and multiparticulate formulations. If the formulation depends on erosion for its mechanisms of release, its release may be accelerated in the presence of food. Gamma scintigraphy can aid in defining this relationship (for methods, see [16–18]). In one study completed in our lab, the in vivo performance of a matrix tablet formulation containing the poorly water soluble drug “Compound A” was determined in dogs [19]. As shown in Table 3, the polymeric matrix tablet formulation was manufactured with the stable isotope of samarium oxide. The tablets were then subjected to the ionizing radiation of a research nuclear reactor, which activated samarium to its gamma-emitting isotope. The tablets were administered to six male beagle dogs of similar age, weight, history, etc., blood samples were serially collected, and plasma Compound A concentrations determined. Through the use of gamma scintigraphy, in vivo disintegration was correlated with the location of the formulation in the gastrointestinal tract. As shown in Table 7, the GET and SITT varied among the six dogs. One explanation for this observation is that a MMC immediately preceded tablet administration in those dogs with a short GET, whereas in dogs with a long GET, the tablets had time to hydrate and swell in the stomach before a MMC swept it into the small intestine.

The radioactivity associated with the matrix tablet was concentrated around the tablet immediately after administration, and dissipated as erosion occurred. As shown in Fig. 10, the matrix tablet in dog #6284 had a short residence time in the stomach (<15 min), while the tablet in dog #6285 remained in the stomach for at least 4

---

**Table 7**

Gastrointestinal transit times for matrix tablets administered to each of six dogs [19]

<table>
<thead>
<tr>
<th>Dog number</th>
<th>6281</th>
<th>6282</th>
<th>6283</th>
<th>6284</th>
<th>6285</th>
<th>6286</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{(0-32)}$ (ng/ml)</td>
<td>2956</td>
<td>373</td>
<td>719</td>
<td>285</td>
<td>4396</td>
<td>1862</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>422</td>
<td>35</td>
<td>81</td>
<td>18</td>
<td>231</td>
<td>182</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>GET* (min)</td>
<td>120</td>
<td>16</td>
<td>39</td>
<td>14</td>
<td>300</td>
<td>180</td>
</tr>
<tr>
<td>Col entb (min)</td>
<td>165</td>
<td>39</td>
<td>79</td>
<td>86</td>
<td>390</td>
<td>315</td>
</tr>
<tr>
<td>SITTc (min)</td>
<td>45</td>
<td>23</td>
<td>40</td>
<td>72</td>
<td>390</td>
<td>135</td>
</tr>
</tbody>
</table>

* GET = gastric emptying time.

b Col. Ent = time entered colon.

c SITT = intest. transit = Col. ent-GET.

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Fig. 10. Scintigraphs of dog #6284 following the administration of a single gamma-emitting matrix tablet. The tablet is shown (A) $T=15$ min, intact in the stomach; (B) $T=75$ min, in the cecum; (C) $T=4–8$ h, in the transverse colon [19].
h (Fig. 11). An estimate of the erosion was made by comparing the amount of radioactivity within and surrounding a “region of interest” (ROI). The erosion of the tablet in dog #6285—which showed a prolonged gastric residence—was considerably more rapid than for the tablet in dog #6284 (which showed a brief stomach residence time) (Fig. 12).

The relationship of GET to “% Erosion” is shown in Fig. 13. Pharmacokinetic and deconvolution analysis correlated the absorption of Compound A with the tablet location. The area under the Compound A plasma concentration vs. time curve (AUC) for the tablet administered to dog #6284—which exhibited...
a SIT of 72 min—was only 285 ng/ml h. In contrast, the tablet remained in the stomach of dog #6285 until erosion was complete; the time for arrival of the first radioactive label at the cecum was 360 min and the AUC was 4396 ng/ml h. Figs. 14 and 15 are composites of plasma Compound A concentrations, tablet erosion, percent Compound A absorbed, and tablet location in the GIT (gastrointestinal tract) for these two dogs. Absorption of Compound A from the matrix tablet was better when erosion of the tablet occurred in the stomach and small intestine. When erosion of the tablet occurred in the colon, Compound A released in the colon did not dissolve (and therefore, was not absorbed).

4.2. Non-eroding, osmotic formulations

Asymmetric membrane (AM) technology enables the formulator to rely on osmotic forces to deliver the drug from a non-eroding dosage form in a controlled manner (for additional examples of osmotic technologies, see Refs. [20,21]). Unlike the eroding matrix tablets, the release of drug from the osmotic formulations should not be sensitive to the grinding/mixing actions of the stomach. For another gamma scintigraphic/pharmacokinetic study from our laboratory [19], the core tablets were prepared by a dry granulation process and made using a conventional tablet press. The AM film coatings consisted of a cellulose acetate/polyethylene glycol...
formulation. AM film coatings were applied onto the core tablets in a side-vented coating pan. The coated tablets were dried in a solvent-compatible oven for 16 h at 40 °C. Formulations consisted of Compound A, glyceryl monolaurate wet granulation onto microcrystalline cellulose, an acid, a calcium salt, and osmogen. The formulation also contained ascorbic acid, calcium carbonate, and lactose. The formulation was administered to six fasted, male beagle dogs. The time for 80% release of Compound A from the AM tablet was 12 h, with no appreciable lag in vitro. The relationship between SITT and AUC is shown in Fig. 16. The reader will note that the short in vivo lag-time of 0.75 h had a significant impact on the AUC for this low solubility compound.

The in vivo performance of CR formulations is often determined by the method of deconvolution [22]. This is valid provided the drug’s pharmacokinetics are linear and time invariant. While “time invariant” usually applies to drug metabolism/transporter modulation, variable solubility and/or permeability of the candidate along the gastrointestinal tract also violates this key assumption. In addition to the application of gamma scintigraphic studies, estimates of the in vivo release for these compounds can be made from tablet recovery studies. Studies that include the recovery of defecated tablets can provide the formulator the opportunity of determining the amount of drug not delivered by the dosage form. By comparing these residuals to the in vitro dissolution results, some idea of the in vitro–in vivo correlation (IVIVC) can be made [23]. As shown in Fig. 17, the in vivo performance of these tablets could be qualitatively compared to their in vitro dissolution.

4.3. Drug degradation/adsorption by colon contents

Basit et al. have reported the importance of drug degradation/adsorption by colon contents when evaluating the fate of a drug released into the large
intestine [24]. We have observed a similar extent of
drug degradation/adsorption in fresh colon contents
of the dog [25]. As shown in Fig. 18, the degra-
dation/adsorption of cimetidine was similar after
incubation in either human or dog colon contents.
Table 8 summarizes the degradation/adsorption of
compounds in controlled release formulations with
complete bioavailability, and some developmental
compounds that exhibited incomplete bioavailability.
This kind of analysis is recommended for any con-
trolled release formulation development when the
duration of release exceeds the SITT.

4.4. Conclusions for controlled release formulations
in the dog

Variability in SITT of monolithic dosage forms
was large. The dog’s short and variable small
intestinal transit time complicated the evaluation
of formulation performance when the compound
exhibited characteristics of LP and/or LS. For a
LP compound, a rapid GETT would result in most
of the drug released in the colon—where its absorption might be slow or incomplete. The result would be similar for the LS compound, since the volume of available water in the colon might be insufficient to dissolve released drug. While compared to matrix tablets, monolithic osmotic formulations reduced the effects of food on release rate, multiparticulates may be the preferred dosage form for companion animals.

The lag-time should also be eliminated when the compound exhibits low solubility and/or low permeability characteristics. This may be accomplished by providing a portion of the total dose in an immediately available form.

Acknowledgements

Drs. M. Jay (University of Kentucky) and R. Beihn (Scintiprox) are acknowledged for assistance with the gamma scintigraphy studies. Dr. J. Fortner DVM is acknowledged for his assistance in performing the colonoscopy studies. Dr. W. Curatolo and Mr. S. Herbig are acknowledged for their support and assistance in the editing of this review. K.A. Norton, J.M. McCarthy and L.A.F. Evans are acknowledged for performing the dog studies. Drs. A. Thombre and M. am Ende, and their associates L. Miller and H. Carter are acknowledged for manufacturing the formulations. Drs. M. Likar and J. Howie are acknowledged for performing the in vitro dissolution tests for many of the formulations. Drs. J.A. Alderman and J.M. Scavone are acknowledged for directing many of the human clinical studies.

References


Table 8

<table>
<thead>
<tr>
<th>Compound</th>
<th>Time (h)</th>
<th>Rinse 1</th>
<th>Rinse 2</th>
<th>Rinse 3</th>
<th>% recovered from rinses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  1  2</td>
<td>0  1  2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% loss in deactivated feces</td>
<td>% loss in fresh feces</td>
<td>% recovered from rinses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>7 14 ND</td>
<td>15 19 ND</td>
<td>86</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Pseudoephedrine HCl</td>
<td>7 15 ND</td>
<td>6 13 ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Compound B</td>
<td>21 59 61</td>
<td>12 42 48</td>
<td>47</td>
<td>67</td>
<td>79</td>
</tr>
</tbody>
</table>

Cimetidine and pseudoephedrine are commercially available as controlled release formulations that have been shown bioequivalent to IR formulations [25].

* Not determined.