Acrylic pH-responsive microparticles for targeted gastrointestinal delivery

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Presentation outline

- Targeted delivery in the GI tract
  - small intestine and large intestine
- Physiology of the GI tract
  - fluid, pH, transit
- Limitations of conventional pH responsive tablets and pellets for GI targeting
- Opportunities for pH-responsive microparticles
- Summary
Targeted delivery in the GI tract – why?

- Bypass the stomach labile actives
- Irritant actives

- Treatment of local diseases
  - Ulcerative colitis
  - Crohn’s disease
  - Irritable bowel syndrome
  - Colonic carcinomas
Ulcerative colitis - inflammation of the mucosa of the large intestine
### Characterisation of GI contents in humans

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Large intestine</th>
<th>Proximal colon</th>
<th>Distal colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duodenum</td>
<td>Jejunum</td>
<td>Ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total fluid volume (ml)</strong></td>
<td>PM</td>
<td>118 ± 82(^1)</td>
<td>212 ± 110(^{*\ast})</td>
<td>187(^{2\ast})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>–</td>
<td>54 ± 41(^*)</td>
<td>11 ± 26(^{\ast})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>45 ± 18</td>
<td>105 ± 72(^*)</td>
<td>13 ± 12(^{\ast})</td>
<td></td>
</tr>
<tr>
<td><strong>Surface tension (mN/m</strong></td>
<td>Fed</td>
<td>35–45(^4)</td>
<td>32.3(^6)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>33.6 ± 5.9(^5)</td>
<td>33.7 ± 2.8(^{*\ast})</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Bile salt concentration (mM)</strong></td>
<td>Fed</td>
<td>0.06(^8)</td>
<td>11.2(^{10})</td>
<td>2–10(^{8})</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>0.2 ± 0.2(^{10})</td>
<td>0.57–5.1(^{11})</td>
<td>2 ± 0.2(^{7})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9 ± 2.9(^{10})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8–5.5(^{11})</td>
<td></td>
</tr>
<tr>
<td><strong>Bile flow rate ((\mu)l/min(^{-1}) kg(^{-1}))</strong></td>
<td>Basal</td>
<td>1–5</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>6–40</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Phospholipids (mM)</strong></td>
<td>Fed</td>
<td>–</td>
<td>3 ± 0.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>0.2 ± 0.07</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>pH(^{14})</strong></td>
<td>Fed</td>
<td>1.0–2.5</td>
<td>–</td>
<td>7.5 ± 0.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>1 × 10(^3)</td>
<td>6.6 ± 0.5</td>
<td>6.4 ± 0.6</td>
<td>–</td>
</tr>
<tr>
<td><strong>Redox potential (mV)</strong></td>
<td>Fed</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Bicarbonate (mM)</strong></td>
<td>Fed</td>
<td>–</td>
<td>6.7(^{17})</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.7(^{19})</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.2(^{21})</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Potassium (mM)</strong></td>
<td>Fed</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Sodium (mM)</strong></td>
<td>Fed</td>
<td>13.4 ± 3.0(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>68 ± 29(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Chloride (mM)</strong></td>
<td>Fed</td>
<td>102 ± 28(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>56 ± 28(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium (mM)</strong></td>
<td>Fed</td>
<td>0.6 ± 0.2(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Magnesium (mM)</strong></td>
<td>Fed</td>
<td>0.15 ± 0.025(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>0.139 ± 0.014(^{10})</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Buffer capacity (mmol/L/pH unit)</strong></td>
<td>Fed</td>
<td>14–28(^{6})</td>
<td>18–30(^{6})</td>
<td>13 ± 6</td>
<td>131 ± 9</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>7–18(^{6})</td>
<td>5.6(^{7}); 4–13(^{10})</td>
<td>–</td>
<td>80 ± 11</td>
</tr>
<tr>
<td><strong>Short chain fatty acids (mmol)</strong></td>
<td>Fed</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2–565(^{2\ast})</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(bacterial amylase)(^{31})</td>
</tr>
<tr>
<td><strong>Amylase (U/ml)</strong></td>
<td>Fed</td>
<td>–</td>
<td>–</td>
<td>13 ± 6</td>
<td>182 ± 26(^{2\ast})</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)McConnell et al, Int J Pharm, 2008
GI pH in humans (median values, n = 39)
### Enteric polymers

<table>
<thead>
<tr>
<th>pH</th>
<th>5.0</th>
<th>5.5</th>
<th>6.0</th>
<th>6.5</th>
<th>7.0</th>
<th>7.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC</td>
<td>HPMC</td>
<td>HPMCAS</td>
<td>HPMCAS</td>
<td>EUDRAGIT S</td>
<td>EUDRAGIT FS</td>
<td>SHELLAC</td>
</tr>
<tr>
<td>HP50</td>
<td>HP55</td>
<td>M</td>
<td>H</td>
<td>E</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>PVAP</td>
<td>CAT</td>
<td>L</td>
<td>CAP</td>
<td>L55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cellulose derivatives**
- HPMC
- HP50
- PVAP

**Methacrylate derivatives**
- HPMCP
- HPMCP HP55
- CAT
- EUDRAGIT L55

**Polyvinyl derivatives**
- HPMCAS
- EUDRAGIT L

**Naturally derived**
Conventional platform formulations

Single Unit

Tablet

- Size: 3-15 mm

Multiple Unit

Pellets or granules

- Size: 0.5 – 2 mm
Mechanism of dissolution of pH-responsive polymers

1) Diffusion of water and hydroxyl ions into the polymer matrix to form a gel layer.
2) Carboxylic acid groups undergo ionization in the gel layer.
3) Disentanglement of polymer chains out of the gel layer and diffusion to the polymer-solution interface.
4) Further ionization of the polymer chains at the polymer-solution interface.
5) Polymer chains diffuse from the interface towards the bulk solution.
Why is targeting in the GI tract difficult – take a look for yourself!!
Gastrointestinal Fluid Volumes

(Gotch et al, 1957; Cummings et al, 1990)
Gender difference – GI fluids in humans

Gotch et al., 1957 36(2):289-96
### GI free fluid volumes and distributions under fasting conditions and 1 h after a meal (n=12)

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Large intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ml)</td>
<td>45</td>
<td>105</td>
<td>13</td>
</tr>
<tr>
<td>Number of fluid pockets</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Fed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) (ml)</td>
<td>686*</td>
<td>54</td>
<td>11</td>
</tr>
<tr>
<td>Number of fluid pockets</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

(*Total fill volume and not only fluid) (Schiller et al, 2005)
Variability in GI pH in humans (n = 39)

(Adapted from Fallingborg et al, 1989)
Variability in GI pH in humans (n = 39)

(adapted from Fallingborg et al, 1989)
Influence of feeding on the gastric emptying of enteric coated tablets (10 mm diameter)

Breakfast 1st tablet administered

Lunch 2nd tablet administered

Dinner 3rd tablet administered

After 12 hours all tablets still in stomach

0900 1130 1330 1600 1830 2100

Time
Plasma profile for 4-ASA delivered from a coated capsule designed to target the colon (volunteer 2)

GET = 79 min
CAT = 405 min

(Tuleu et al, 2002)
Plasma profile for 4-ASA delivered from a coated capsule designed to target the colon (volunteer 5)

Plasma concentration (ug/ml)

0 0.4 0.8 1.2 1.6 2

Time (h)

0 2 4 6 8 10 12

GET = 6 min   CAT = 178 min   Capsule voided!

(Tuleu et al, 2002)
The problem of lack of release is not restricted to single unit systems (in vivo behaviour of two different coated pellet formulations)

First appearance of pellets in caecum

Bacteria triggered system

pH triggered system

[McConnell et al., 2008]
Opportunities for enteric (pH-responsive) microparticles (sub 100um)
Potential advantages of enteric microparticles

- Particles suspended in gastric contents due to small size
- Rapid gastric emptying
- Rapid particle dissolution
- Ideal for drugs with poor solubility (solid dispersions)
- Improved GI targeting and more reproducible pharmacokinetic profiles
Methods to prepare microparticles

- Coacervation
- Extrusion-spheronisation
- Centrifugal Extrusion
- Spray drying
- Solvent evaporation
- Spray-freezing into Liquid
- Spray Freeze-drying
<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coacervation</td>
<td>• More effective to produce microcapsules</td>
<td>• Control of pH and several other parameters</td>
</tr>
<tr>
<td></td>
<td>• Wide range of particle size</td>
<td>• Particles need stabilization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Removal of residual solvents can be difficult</td>
</tr>
<tr>
<td>Extrusion-spheronisation</td>
<td>• Conducive to industrial scale-up</td>
<td>• Confined to large size particles</td>
</tr>
<tr>
<td>Centrifugal Extrusion</td>
<td>• Conducive to industrial scale-up</td>
<td>• Large size particles</td>
</tr>
<tr>
<td></td>
<td>• Efficient for microcapsule production</td>
<td></td>
</tr>
<tr>
<td>Spray drying</td>
<td>• Conducive to industrial scale-up</td>
<td>• Increased cost at lab-scale</td>
</tr>
<tr>
<td></td>
<td>• Good reproducibility</td>
<td>• No well-established methods using enteric microparticles</td>
</tr>
<tr>
<td></td>
<td>• Precise control of parameters</td>
<td>• Heat may inactivate sensitive products</td>
</tr>
<tr>
<td>Solvent evaporation</td>
<td>• Simplicity</td>
<td>• Industrial scale up</td>
</tr>
<tr>
<td></td>
<td>• High loading efficacy</td>
<td>• Solvent residues</td>
</tr>
<tr>
<td></td>
<td>• Low cost at the lab level</td>
<td>• Solvents consumption</td>
</tr>
<tr>
<td>Spray-freezing into Liquid</td>
<td>• Tight control of parameters and particle size</td>
<td>• The use of liquid nitrogen</td>
</tr>
<tr>
<td></td>
<td>• Suitable for heat-labile drugs</td>
<td>• High porosity of polymeric matrix</td>
</tr>
<tr>
<td></td>
<td>• Single step process</td>
<td></td>
</tr>
<tr>
<td>Spray Freeze-drying</td>
<td>• Tight control of parameters and particle size</td>
<td>• Two-stage process</td>
</tr>
<tr>
<td></td>
<td>• Suitable for heat-labile drugs</td>
<td>• Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Schematic of emulsification / solvent evaporation method
Emulsification of drug and polymer solution in liquid paraffin

solvent diffuses from dispersed phase to continuous phase and evaporates

microparticles are separated through filtration and washed with n-hexane.

droplets solidify into microparticles
Preparation conditions
- Temperature
- Pressure
- Agitation speed
- Geometry of propeller and vessel

Dispersed Phase
- Solvent
- Co-solvents
- Polymer(s)
- Drug
- Poregen

Continuous phase
- Non-solvent
- Surfactant
- Anti-foam

Process parameters
- Drug: polymer ratio
- Dispersed phase: continuous phase volume ratio
- Viscosities of the two phases
- Concentration of surfactant(s)
- Concentration of polymer solution

Preparation conditions
- Temperature
- Pressure
- Agitation speed
- Geometry of propeller and vessel

Microsphere characteristics
- Median and average size
- Polydispersity
- Encapsulation efficiency
- Yield
- Bulk and actual density
- Drug release
<table>
<thead>
<tr>
<th>Polymer type</th>
<th>$n_1:n_2$</th>
<th>MW</th>
<th>Soluble at pH &gt;</th>
<th>Acid value (KOH/g)</th>
<th>Free $\text{–COOH}$ group (per 100,000 Da)</th>
<th>Coating solution viscosity (mm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUDRAGIT L</td>
<td>1:1</td>
<td>135,000</td>
<td>6.0</td>
<td>300-330</td>
<td>537</td>
<td>10-24</td>
</tr>
<tr>
<td>EUDRAGIT S</td>
<td>1:2</td>
<td>135,000</td>
<td>7.0</td>
<td>180-200</td>
<td>349</td>
<td>22-52</td>
</tr>
</tbody>
</table>
Glass transition of polymer films cast from ethanol as measured using DMA

**EUDRAGIT S**
- Tg (dry): [110°C, 120°C]
- Tg (wet): [70°C, 80°C]

**EUDRAGIT L**
- Tg (dry): [140°C, 150°C]
- Tg (wet): [20°C, 30°C]
Prednisolone-loaded Eudragit microparticles

Eudragit L

Eudragit S
Properties of Eudragit microparticles

<table>
<thead>
<tr>
<th></th>
<th>Eudragit L microparticles</th>
<th>Eudragit S microparticles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>96.4</td>
<td>97.1</td>
</tr>
<tr>
<td>Encapsulation efficiency (%)</td>
<td>86.4</td>
<td>90.0</td>
</tr>
<tr>
<td>Size $d_{v(0.5)}$ ($\mu$m)</td>
<td>31.3</td>
<td>50.1</td>
</tr>
<tr>
<td>Density (g/cm$^3$)</td>
<td>1.26</td>
<td>1.22</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.16</td>
<td>1.15</td>
</tr>
<tr>
<td>Flow</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

[Kendall et al., 2009]
In-vitro dissolution: Eudragit L microparticles for small intestinal targeting

![Graph showing prednisolone release from Eudragit L (5:1) particles (pH 1.2-6.8)]
In-vitro dissolution: Eudragit S microparticles for colonic targeting

Prednisolone release from Eudragit S microparticles vs. S coated tablet (pH 1.2-7.4)
In-vitro dissolution: release rate can be controlled by drug loading

Prednisolone release from S microparticles (different drug loadings)

- S100/prednisolone (2.5:1)
- S100/prednisolone (3:1)
- S100/prednisolone (5:1)
- S100/prednisolone (10:1)
- S100/prednisolone (20:1)
Dipyridamole loaded microparticles

[Nilkumhang et al., 2009]
Acridine orange-loaded microparticles

Heterogeneous micromatrix

[Nilkumhang et al., 2009]
Riboflavin-loaded microparticles

[Nilkumhang et al., 2009]
Major problem with enteric microparticles – premature drug release in acid

- Relationship between drug molecular weight, acid solubility and particle size on drug release from enteric microparticles in acid
Drug-loaded Eudragit L microparticles
Drug-loaded Eudragit S microparticles
Eudragit S microparticles

The School of Pharmacy
University of London

Drum released (%)

Time (min)

pH 1.2

pH 7.4

Indomethacin
Naproxen
Ketoprofen
Salicylic acid
Paracetamol
Prednisolone
Budenoside
Amprenavir
Bendrofluamide
Cinnarizine
Dipyridamole
Eudragit L microparticles
Relationship between parameters - multiple linear regression

\[ \% \text{ release} = 65.346 - 0.137 \text{MW} + 6.3 \log (\text{Sol}) - 0.01 r^2 + 1.82P \]

where \( \text{MW} \) = drug molecular weight (Da), \( \log (\text{Sol}) \) = logarithm of drug saturation solubility in the acidic medium at 37 °C assessed in mg/L, \( r \) = Median diameter of microparticles (µm) and \( P \) is a constant relating to the polymer, \( P = 0 \) for Eudragit S and \( P = 1 \) for Eudragit L.

- Drug molecular weight (cut-off of approx 300Da) is more important than drug solubility in acid or microparticle size in controlling drug release in acid
In vivo performance of Eudragit microparticles in rats
Mean pharmacokinetic profiles for the different formulations (n=5 for each)
Rat and human gut

Stomach

Small intestine

Caecum

Colon
Fluid Volumes in Man

(Gotch et al, 1957; Cummings et al, 1990)
Fluid Volumes in Man and Rat

(Gotch et al, 1957; Cummings et al, 1990; McConnell et al., 2008)
Fluid Volumes in rat

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.5</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>1.0</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>1.5</td>
</tr>
</tbody>
</table>

(McConnell et al., 2008)
Gastrointestinal pH in rats

McConnell et al., 2008 Journal of Pharmacy and Pharmacology

(Fed Rats (n=5))
(Fasted Rats (n=5))

(McConnell et al., 2008)
Potential applications of enteric microparticles

- Particularly suitable for poorly soluble compounds
- Application to poorly soluble basic compounds – overcome precipitation in the small intestine
- Stomach unstable/irritant compounds with absorption windows in the proximal small intestine
- Or those to be delivered to the colon
- Ability to produce tailored release profiles
- Ideal for use for pediatric applications
Conclusions

- The GI tract is a heterogeneous environment

- Key GI variables such as fluid volume, transit times and pH can impact on enteric dosage form performance

- Enteric microparticles should have more reliable in vivo behaviour than coated tablets and pellets

- Size does matter.............