Literature review on swallowability of oral solid dosage forms in children
Fang Liu
University of Hertfordshire
Overview

- Outcomes of a systematic literature review on swallowability of oral solid dosage forms in children
- Analysis in recently approved paediatric products
Search strategy

- Databases: Pubmed, Scopus, and Embase
- Keywords: (“paediatric” OR “pediatric” OR “children” OR “infant” OR “newborn” OR “adolescent” OR “teens” OR “youth” OR “teenagers”) AND ("oral formulation" OR "oral dosage form") AND ("Satisfaction" OR "acceptance" OR "preference" OR "approval" OR "acceptability" OR "swallow" OR "palatability")
- Date: From the start of the source to May 2016
- Study selection: English, paediatric population, swallowing related
A total of 13 studies were identified on swallowability of oral solid dosage forms in children:

- Tablet (> 5 mm): 3
- Mini-tablet (1-4 mm): 7
- Capsules: 3
## Search results - tablets

<table>
<thead>
<tr>
<th>Formulation factors</th>
<th>Age</th>
<th>Disease status</th>
<th>Methodology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7mm</td>
<td>Round</td>
<td>Uncoated</td>
<td>Ketoprofen 25 mg</td>
<td>1-9 years</td>
</tr>
<tr>
<td>5mm and 8mm</td>
<td>Round</td>
<td>Film coated</td>
<td>Levamisole 5, 10, 25 or 50 mg</td>
<td>2-11 years</td>
</tr>
<tr>
<td>7mm</td>
<td>Cylinder</td>
<td>Wax coated</td>
<td>placebo tablets</td>
<td>6-11 years</td>
</tr>
</tbody>
</table>
## Search results – mini-tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Size</th>
<th>Shape</th>
<th>Coating</th>
<th>Drug content</th>
<th>Age</th>
<th>Disease status</th>
<th>Methodology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-tablet</td>
<td>3mm</td>
<td>Round</td>
<td>uncoated</td>
<td>Placebo (single tablet)</td>
<td>2-6 years</td>
<td>Attend outpatient clinic</td>
<td>Observation</td>
<td>(Thomson, Tuleu et al. 2009)</td>
</tr>
<tr>
<td></td>
<td>2mm</td>
<td>Round</td>
<td>Uncoated</td>
<td>Placebo (single tablet)</td>
<td>6 months – 6 years</td>
<td>Attended hospital</td>
<td>Observation</td>
<td>(Spomer, Klingmann et al. 2012)</td>
</tr>
<tr>
<td></td>
<td>2mm</td>
<td>Round</td>
<td>Coated and uncoated</td>
<td>Placebo (single tablet)</td>
<td>6 months – 6 years</td>
<td>Attended hospital</td>
<td>Observation</td>
<td>(Klingmann, Spomer et al. 2013)</td>
</tr>
<tr>
<td></td>
<td>2mm</td>
<td>Round</td>
<td>Enteric coated</td>
<td>Pancrelipase-e</td>
<td>6-30 months</td>
<td>With cystic fibrosis</td>
<td>Questionnaire</td>
<td>(Van de Vijver, Desager et al. 2011)</td>
</tr>
<tr>
<td></td>
<td>4mm</td>
<td>Round</td>
<td>Uncoated</td>
<td>Placebo (single tablet)</td>
<td>1-4 years</td>
<td>Healthy</td>
<td>Observation</td>
<td>(van Riet-Nales, de Neef et al. 2013)</td>
</tr>
<tr>
<td></td>
<td>2mm</td>
<td>Round</td>
<td>Uncoated</td>
<td>Placebo (single tablet)</td>
<td>2-28 days</td>
<td>Attended hospital</td>
<td>Observation</td>
<td>(Klingmann, Seitz et al. 2015)</td>
</tr>
<tr>
<td></td>
<td>2mm and 3mm</td>
<td>Round</td>
<td>Uncoated</td>
<td>Placebo (5-10 tablets with jelly)</td>
<td>2-3 years</td>
<td>Attended health clinics</td>
<td>Observation</td>
<td>(Kluk, Sznitowska et al. 2015)</td>
</tr>
</tbody>
</table>
## Search results – capsules

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Formulation factors</th>
<th>Age</th>
<th>Disease status</th>
<th>Methodology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasing sizes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gelatin capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncoated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3-13 years</td>
<td>HIV infection</td>
<td>Observation (training effects)</td>
<td>(Czyzewski, Runyan et al. 2000)</td>
</tr>
<tr>
<td></td>
<td>Increasing sizes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gelatin capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncoated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4-21 years</td>
<td>HIV infection</td>
<td>Observation (training effects)</td>
<td>(Garvie, Lensing et al. 2007)</td>
</tr>
<tr>
<td></td>
<td>#4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gelatin capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enteric coated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typhoid vaccine</td>
<td>4-12 years</td>
<td>Healthy</td>
<td>Observation</td>
<td>(Mekmullica and Pancharoen 2003)</td>
</tr>
</tbody>
</table>
Challenges in assessment methodology

- Study design
- Population
- Formulation factors
- Swallowability criteria
Study design

- Questionnaires
- Interviews
- Clinical trials
- Observational study
Population

- **Age groups**

<table>
<thead>
<tr>
<th>Preterm newborn infants</th>
<th>Term newborn infants</th>
<th>Infants and toddlers (1m-2y)</th>
<th>Pre-school children</th>
<th>School children</th>
<th>Adolescents (12-18y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-28 days</td>
<td>0-28 days</td>
<td>1 months – 2 years</td>
<td>2-5 years</td>
<td>6 – 11 years</td>
<td>12 – 18 years</td>
</tr>
</tbody>
</table>

- Healthy vs with particular diseases
Formulation factors

- Size
- Shape
- Coating
- Taste/smell
- Mouth feel
- Number
Swallowability criteria

- Do we need a set criteria?
- How can we vary the criteria for different cases, e.g. particular diseases, different formulations?
- Chewing
- Risk of choking/coughing
An analysis on recently approved paediatric products

- A database search on EMA approved pharmaceutical products was conducted
- Date: Jan 2007 to May 2016
- All approved products for oral use in paediatric populations (0 – 18 years) were selected
  - Different dose strengths were treated as separate products

![Number of products](chart.png)
Minimum age approved

Number of products

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>10</td>
</tr>
<tr>
<td>1 m - 2 y</td>
<td>13</td>
</tr>
<tr>
<td>2-5 y</td>
<td>17</td>
</tr>
<tr>
<td>6-11 y</td>
<td>11</td>
</tr>
<tr>
<td>12-18 y</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
</tr>
</tbody>
</table>

* Newborn: include products for paediatric use but no age specification
Products for newborns

- Tablet IR swallowable: 1
- Tablet dispersible: 0
- Capsule: 1
- Oral liquid ready made: 2
- Sachet with...: 3
- Total: 10

Number of products
Products for 1 month – 2 years

Tablet shapes

Tablet sizes (oblong types)
Min length: 14.2 mm
Max length: 17.6 mm
Products for 2 - 5 years

Tablet shapes

Number of products

Tablet sizes (round)
Diameter: 7 mm

Tablet sizes (oblong types)
Min length: 9.3 mm
Max length: 19.6 mm

European Paediatric Formulation Initiative
**Products for 5-11 years**

**Tablet shapes (include MR)**

- Number of products:
  - Tablet IR swallowable: 3
  - Tablet MR: 4
  - Tablet dispersible: 0
  - Capsule: 3
  - Oral liquid ready made: 0
  - Sachet with powder/granules: 1
  - Total: 11

**Tablet sizes (round)**

- Diameter: 7 mm

**Tablet sizes (oblong types)**

- Min length: 12.3 mm
- Max length: 16.5 mm

---

European Paediatric Formulation Initiative
Products for 12-18 years

Tablet shapes (include MR)

- Number of products

Tablet sizes (round)
- Min diameter: 6 mm
- Max diameter: 10 mm

Tablet sizes (oblong types)
- Min length: 8.1 mm
- Max length: 22 mm
Thank you!