AGE-APPROPRIATE ORAL PEDIATRIC FORMULATIONS IN HOSPITALS
– EVALUATION OF THE SUITABILITY OF PRINTING TECHNOLOGIES IN MEETING PATIENT NEEDS

13.9.2022 / Maria Rautamo
BACKGROUND

Pediatric population

Age range
Drug acceptability
Enteral feeding tube

Specific needs

Personalized doses
Safety of excipients
Age-appropriate dosage forms
Lack of age-appropriate oral pediatric formulations

**Actions to improve situation**

**Authorities**
- Improved legislation
  - EU Paediatric regulation

**Industry Pharmacy Academia**
- Drug development
  - Indications
  - Dosage forms

**Actions to manage situation**

**Healthcare**
- Unlicensed drug use
  - Pharmaceutical preparation
    - Age-appropriate dosage forms
  - Drug manipulation
    - E.g. splitting, crushing, dispersing
  - Drugs with special license
    - Age-appropriate dosage forms
  - Off-label drug use
    - Deviating from SmPC
printing Technologies in Drug Manufacturing

- **Inkjet-based methods**
  - Binder jetting / Drop-on-powder
  - Continuous inkjet printing
  - Drop-on-demand
  - Semi-solid extrusion
  - Piezoelectric inkjet printing

- **Extrusion-based methods**
  - Fused deposition modeling
  - Direct powder extrusion

- **Laser-based methods**
  - Selective laser sintering
  - Stereolithography

- **Study III**

- **Semi-solid extrusion printing**
  - Formulation of printing mixture
  - CAD design
  - Printing
  - Drying

- **Inkjet printing**
  - Preparation of substrate
  - CAD design
  - Formulation of printing ink
  - Printing
  - Drying
  - Cutting of dosage units

(modified from Goole & Amighi, 2016)

Tailoring of drug products

- dose
- dosage forms
- shape
- size
- color
- flavor
1. To explore the oral drug administration practices at pediatric hospital wards, with focus on drug manipulation habits, experienced challenges, and methods used to mitigate existing problems (Study I)

2. To investigate the perceptions of healthcare professionals in a tertiary university hospital about oral printed formulations for pediatric patients (Study II)

3. To compare the pharmaceutical quality (content uniformity, dose accuracy and stability) of printed orodispersible films to oral powders in unit dose sachets and to evaluate the suitability of inkjet and semi-solid extrusion printing methods for on-demand preparation in hospital pharmacies compared to current manufacturing methods (Study III)

RESEARCH QUESTION

• Can orally administered age-appropriate formulations for children be produced at hospital pharmacies via printing technologies to meet patient needs?
# METHODS (STUDY I AND II)

Qualitative study method - Focus group discussions

## PARTICIPANTS

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phycisians, nurses and clinical pharmacists working at the Department of</td>
<td>Children and Adolescents at HUS Helsinki University Hospital</td>
</tr>
<tr>
<td>Purposive selection of participants:</td>
<td>representation of different pediatric subspecialties</td>
</tr>
</tbody>
</table>

## ETHICAL ASPECTS

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
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<tbody>
<tr>
<td>Participation was voluntary, written informed consent</td>
<td></td>
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<tr>
<td>Ethical approval was received from HUS Ethics Committee</td>
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</tbody>
</table>

## DATA COLLECTION

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus group discussions between May and September 2018</td>
<td></td>
</tr>
<tr>
<td>Five groups with 3 – 5 participants</td>
<td></td>
</tr>
<tr>
<td>Interview guide</td>
<td></td>
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<tr>
<td>Introduction to the topic including a video clip about inkjet printing</td>
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</table>

## DATA ANALYSIS

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inductive content analysis by two investigators separately</td>
<td>Coding</td>
</tr>
<tr>
<td>• Grouping of codes into categories and subcategories</td>
<td></td>
</tr>
</tbody>
</table>
METHODS (STUDY III)

Quantitative study method – Comparison of production methods

Target doses of warfarin sodium: 0.1, 0.5, 1 and 2 mg

Drug content
- UV/Vis, 207 nm
- uniformity of content (Ph. Eur. 2.9.6)
- uniformity of dosage units (Ph. Eur. 2.9.40)
- stability (28 days)

Dose recovery from nasogastric tubing

Recording of manufacturing times
• Orodispersible and liquid dosage forms suitable for most pediatric patients
• Tablets and capsules unsuitable because of insufficient dose flexibility and need to modify the dose
### Key Results (Study II)

<table>
<thead>
<tr>
<th>Drug substance or medical condition</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>Need for personalized doses of oral drug products</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Current lack of oral drug products for pediatric patients</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Need for better options to currently available dosage forms</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Need for better options to currently available dosage forms</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Need for orodispersible dosage form</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Need for personalized doses of oral drug products</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Current lack of oral drug products for pediatric patients</td>
</tr>
<tr>
<td>Strong opiates, e.g., morphine and oxycodone</td>
<td>Need for better options to currently available dosage forms</td>
</tr>
<tr>
<td>Current lack of oral dosage forms for pediatric patients</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Need for personalized doses of oral drug products</td>
</tr>
<tr>
<td>HIV</td>
<td>Need for combination products and personalized doses</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>Need for combination products and personalized doses</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Need for combination products and personalized doses</td>
</tr>
</tbody>
</table>
KEY RESULTS (STUDY III)

- Orodispersible films fulfilled the test of content uniformity for formulations of 0.5, 1 and 2 mg
- Semi-solid extrusion printing produced more uniform dosage units than inkjet printing and manual preparation of dose powders
- One-month stability
- Administration through nasogastric tubing
- Imprinting of identification in form of QR code

Orodispersible film imprinted with a QR code

Printed orodispersible films produced by:
(A) semi-solid extrusion printing;
(B) inkjet printing.

Doses and dimensions of formulations from left to right: 0.1 mg / 5 x 5 mm, 0.5 mg / 11.2 x 11.2 mm, 1 mg / 15.8 x 15.8 mm, 2 mg / 22.4 x 22.4 mm.
## SUMMARY OF KEY RESULTS AND DISCUSSION (STUDY II AND III)

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Benefits</th>
<th>Concerns</th>
<th>Prerequisites</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Safety</strong></td>
<td>Precise dose</td>
<td>Dose accuracy and quality control</td>
<td>Verification of drug content and dose accuracy</td>
<td>Qualification of equipment (OQ, PQ) Quality control prior delivery</td>
</tr>
<tr>
<td></td>
<td>Imprinting identification directly onto dosage form</td>
<td>Identification of dosage units at hospital wards</td>
<td>Visually different dosage units Identification information</td>
<td>Unit dose packaging Barcode in label Barcode medication administration</td>
</tr>
<tr>
<td></td>
<td>Stability</td>
<td>Shelf-life and storage conditions</td>
<td>Storage in room temperature</td>
<td>Blister packaging Stability studies</td>
</tr>
<tr>
<td><strong>Drug Administration</strong></td>
<td>Personalized doses and formulations</td>
<td>Size of formulation</td>
<td>Small size</td>
<td>Design of formulation according to patient needs</td>
</tr>
<tr>
<td></td>
<td>Ease of drug administration</td>
<td>Administration through feeding tubes</td>
<td>Possibility to dissolve or disperse formulation No blockage of feeding tubes</td>
<td>Formulation development Verification of dose recovery from enteral feeding tubes</td>
</tr>
<tr>
<td><strong>Production and Delivery on-Demand</strong></td>
<td>Delivery of new products if patient’s dose is changed</td>
<td>Length of production time</td>
<td>Process lead times must meet customer needs</td>
<td>Process optimization • prefabricated ink/substrate • printing time • drying time</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Cost savings</td>
<td>Increased production costs</td>
<td>Cost-efficiency</td>
<td>Cost analysis</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• The availability of drug therapies for children can be improved by developing age-appropriate drug formulations that enable personalized dosing, are easy to administer and acceptable by children, do not require drug manipulation, can be administered through feeding tubes and ensure continuity of treatment unchanged at patient discharge

• An ideal drug formulation would be small, stable at room temperature, easy to identify and accessible to hospital wards on-demand

• The interviewed healthcare professionals showed a positive attitude towards using printing technologies at hospital pharmacies

• Orodispersible films produced by inkjet and semi-solid extrusion printing methods are potential alternatives to the manual preparation of dose powders

• Future development to ensure the quality, identification and production on-demand is required
FUTURE PERSPECTIVES
• Rautamo, M.; Kvarnström, K.; Sivén, M.; Airaksinen, M.; Lahdenne, P.; Sandler, N. A focus group study about oral drug administration practices at hospital wards - Aspects to consider in drug development of age-appropriate formulations for children. Pharmaceutics 2020, 12, 109 (Open Access)

• Rautamo, M.; Kvarnström, K.; Sivén, M.; Airaksinen, M.; Lahdenne, P.; Sandler, N. Benefits and prerequisites associated with the adoption of oral 3D-printed medicines for pediatric patients: A focus group study among healthcare professionals. Pharmaceutics 2020, 12, 229 (Open Access)

• Öblom, H.; Sjöholm, E.; Rautamo, M.; Sandler, N. Towards printed pediatric medicines in hospital pharmacies: Comparison of 2D and 3D-printed orodispersible warfarin films with conventional oral powders in unit dose sachets. Pharmaceutics 2019, 11, 334 (Open Access)
THANK YOU!

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