4th Nordic Conference on Paediatric Medicines

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

13.9.2022 / Maria Rautamo

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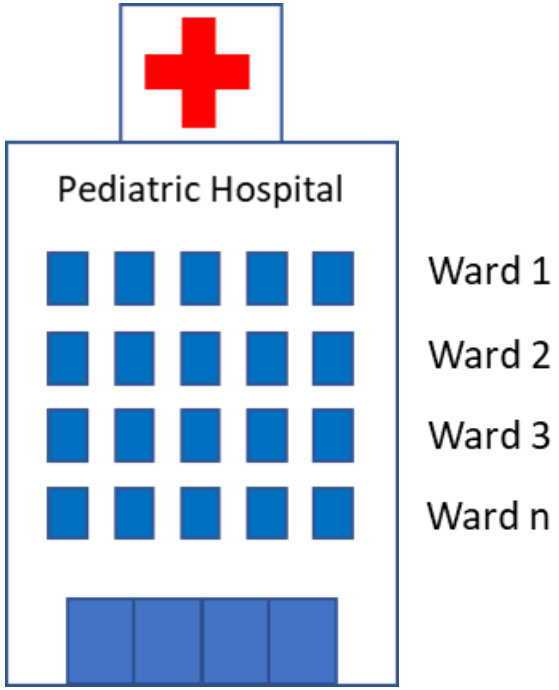
HUS & HELSINGFORS UNIVERSITET I SAMARBETE
A COLLABORATION BETWEEN HUS & UNIVERSITY OF HELSINKI

BACKGROUND

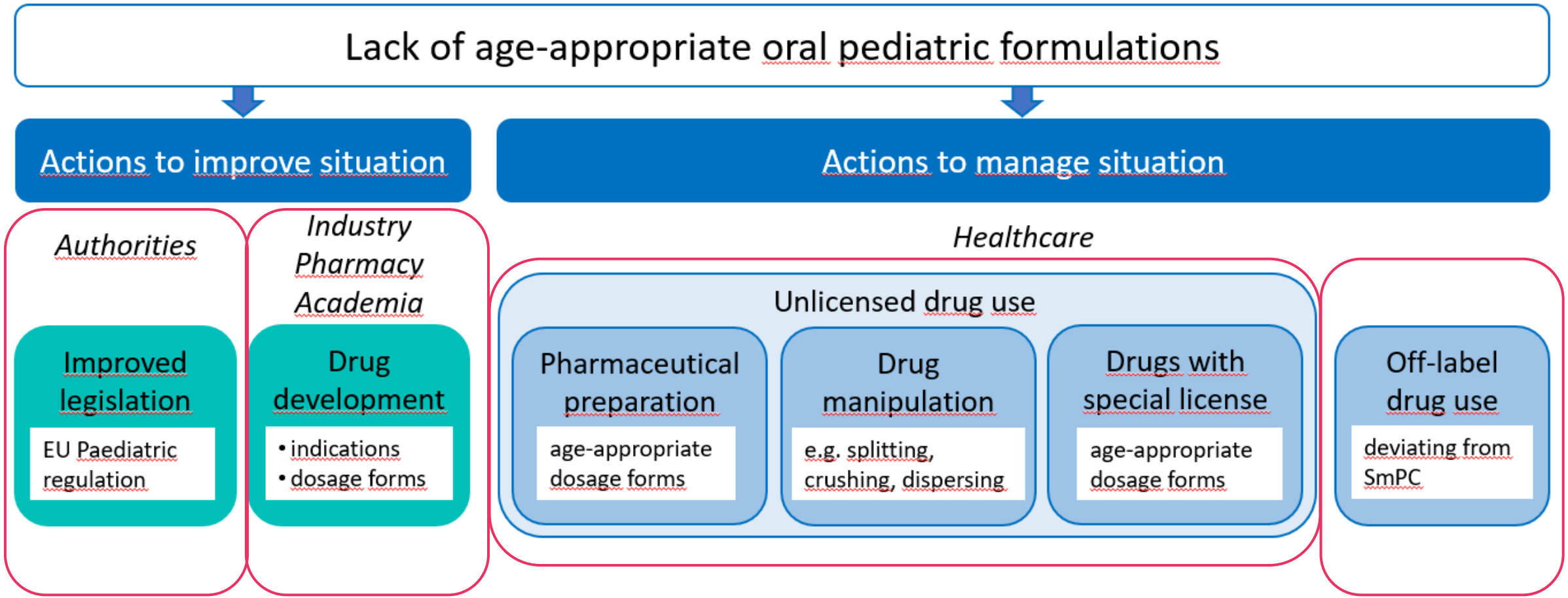


Pediatric population

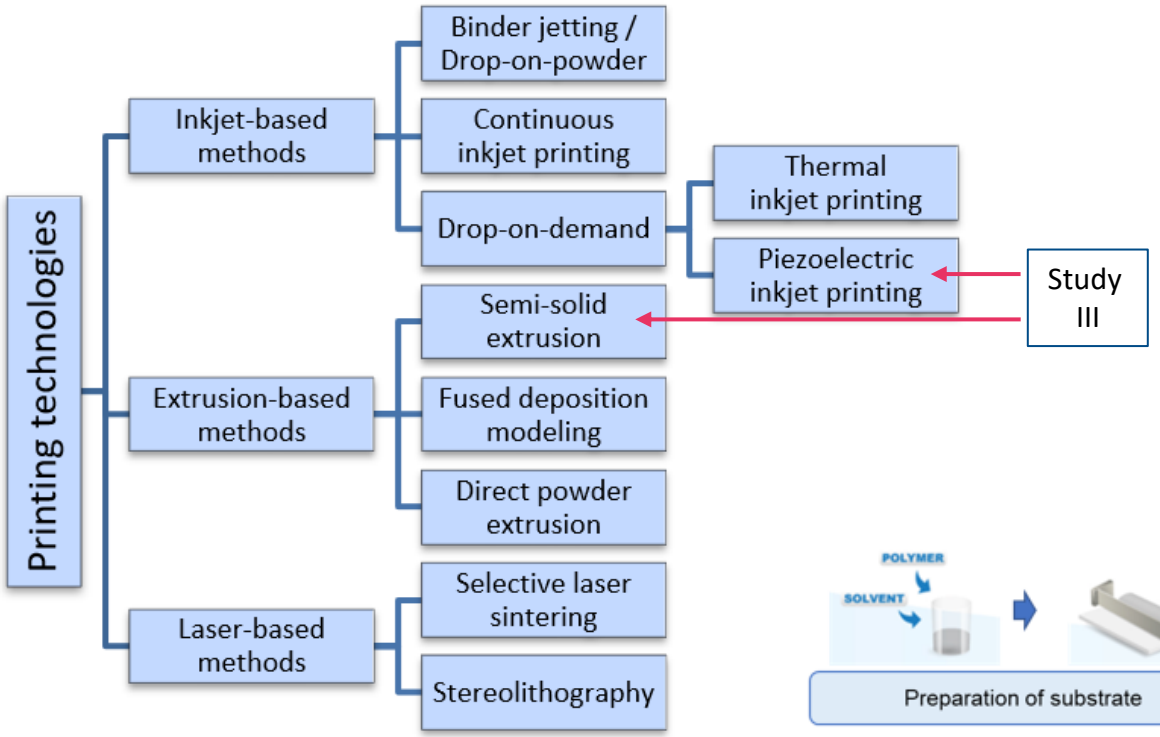
- Age range
- Drug acceptability
- Enteral feeding tube

Specific needs

- Personalized doses
- Safety of excipients
- Age-appropriate dosage forms

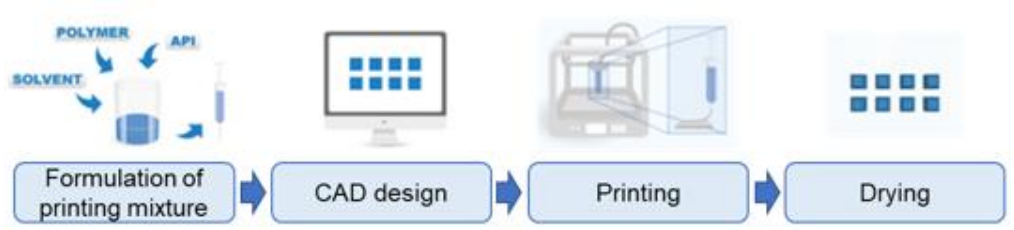

Lack of age-appropriate oral pediatric formulations
Actions to improve situation
Actions to manage situation
Authorities
Industry
Pharmacy
Academia
Healthcare
Improved legislation
EU Paediatric regulation
Drug development
• indications
• dosage forms
Unlicensed drug use
Pharmaceutical preparation
age-appropriate 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



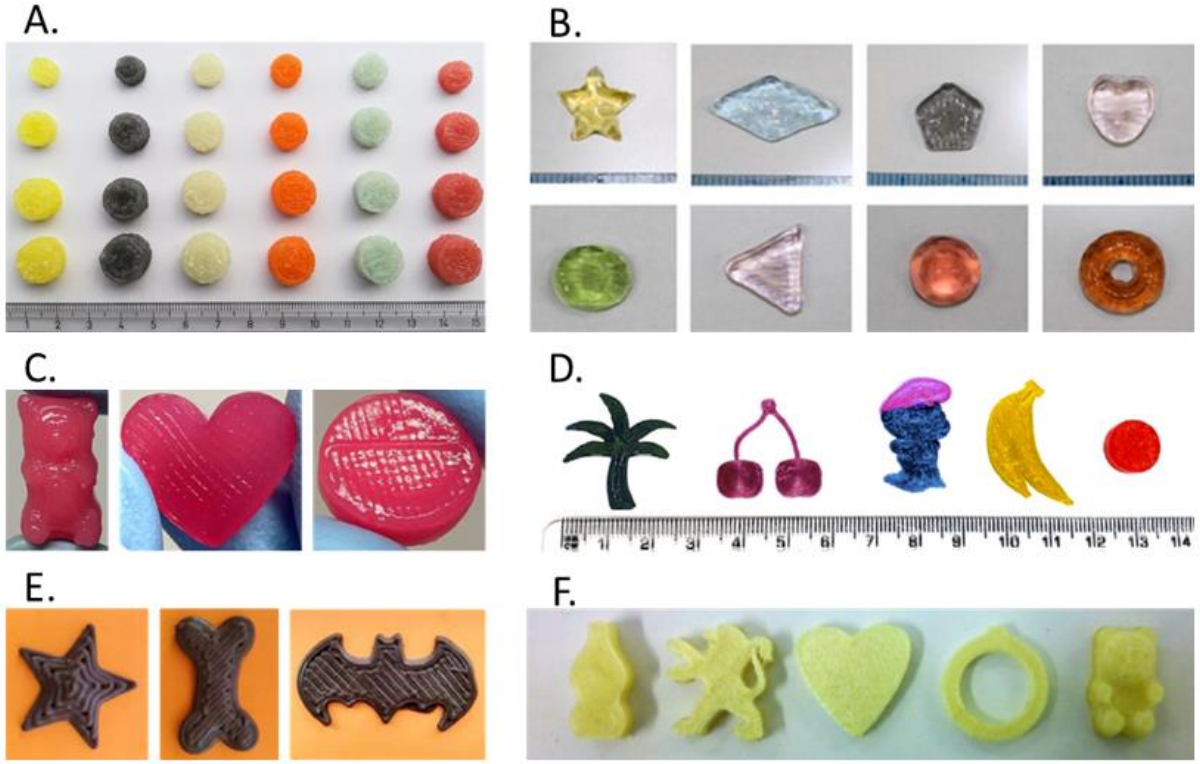
(modified from Goole & Amighi, 2016)

Semi-solid extrusion printing



Inkjet printing

PRINTED ORAL PEDIATRIC FORMULATIONS



Various shapes of printed dosage forms created for the target population of children to improve drug acceptability. Reproduced with permission from A. (Goyanes et al. 2019b), B. (Tagami et al. 2021), C. (Herrada-Manchón et al. 2020), D. (Tabriz et al. 2021), E. (Karavasili et al. 2020), and F. (Scoutaris et al. 2018).

Tailoring of drug products

- dose
- dosage forms
- shape
- size
- color
- flavor

RESEARCH QUESTION

- **Can orally administered age-appropriate formulations for children be produced at hospital pharmacies via printing technologies to meet patient needs?**

STUDY OBJECTIVES

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)**

METHODS (STUDY I AND II)

Qualitative study method - Focus group discussions

PARTICIPANTS
Phycisians, nurses and clinical pharmacists working at the Department of Children and Adolescents at HUS Helsinki University Hospital
Purposive selection of participants: representation of different pediatric subspecialties

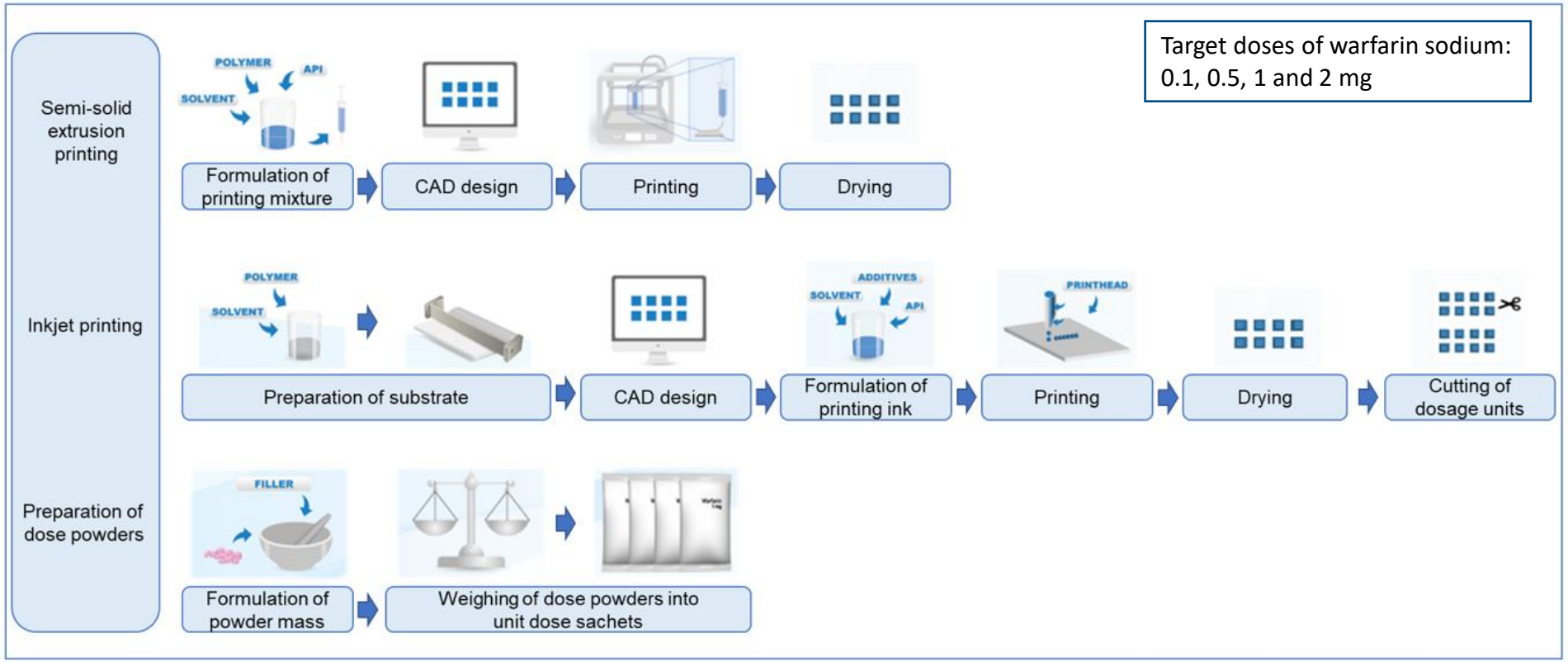
ETHICAL ASPECTS
Participation was voluntary, written informed consent
Ethical approval was received from HUS Ethics Committee

DATA COLLECTION
Focus group discussions between May and September 2018
Five groups with 3 – 5 participants
Interview guide
Introduction to the topic including a video clip about inkjet printing

DATA ANALYSIS
Inductive content analysis by two investigators separately • Coding • Grouping of codes into categories and subcategories

METHODS (STUDY III)

Quantitative study method – Comparison of production methods



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

Permormed tests:

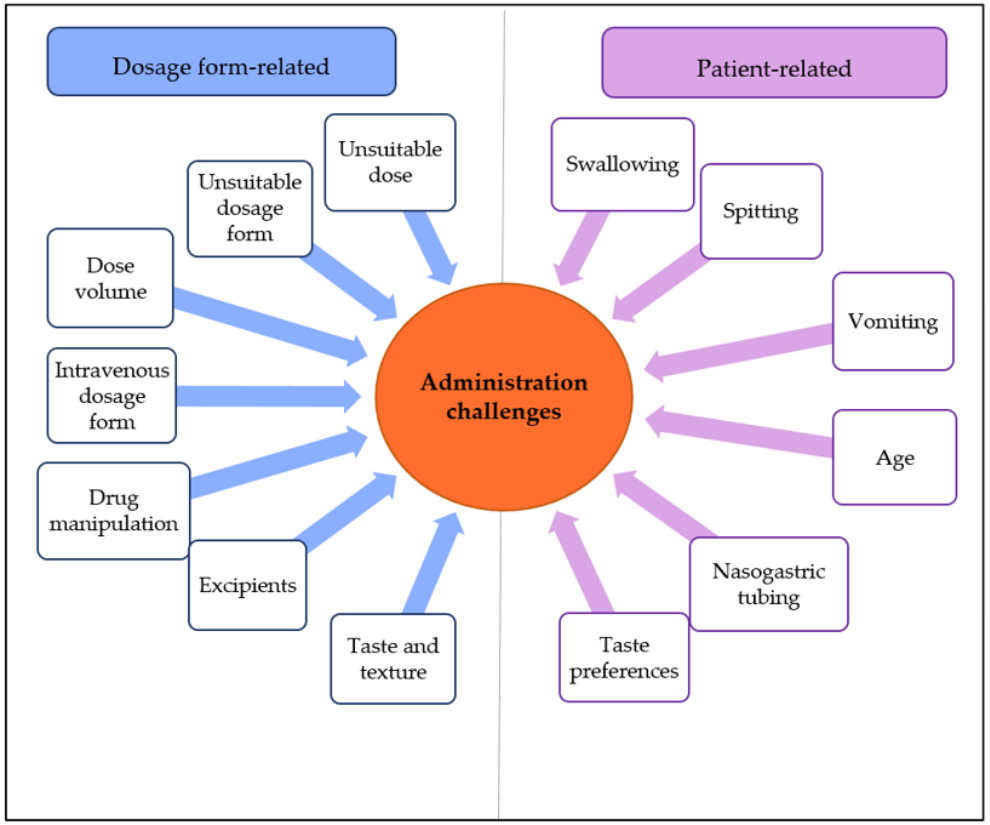
Drug content
- UV/Vis, 207 nm
- uniformity of content (Ph. Eur. 2.9.6)
- uniformity of dosage units (Ph. Eur. 2.9.40)
- stability (28 days)

Dose recovery from nasogastric tubing

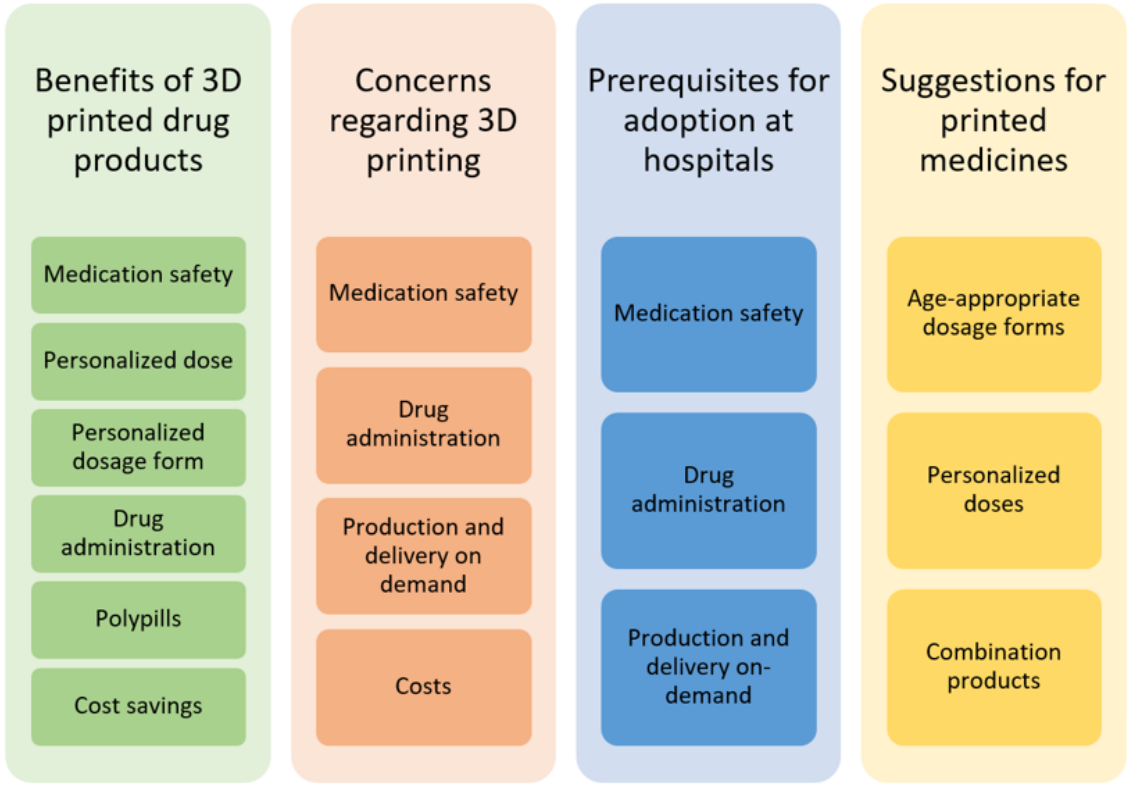
Recording of manufacturing times

KEY RESULTS (STUDY I)

- 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)

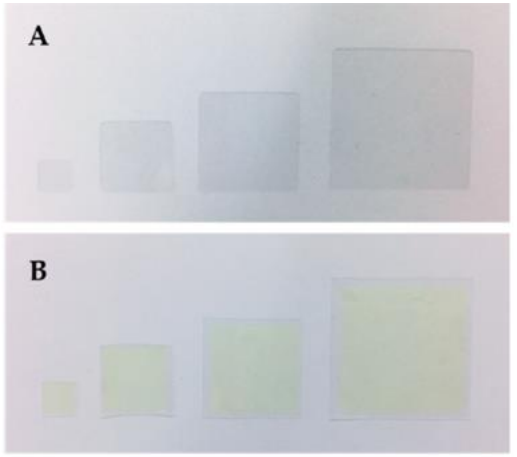


Drug substance or medical condition	**Reason**
Esomeprazole	Need for personalized doses of oral drug products
Ketamine	Current lack of oral drug products for pediatric patients
Midazolam	Need for better options to currently available dosage forms
Paracetamol	Need for better options to currently available dosage forms
Risperidone	Need for orodispersible dosage form
Warfarin	Need for personalized doses of oral drug products
Electrolytes	Current lack of oral drug products for pediatric patients
Strong opiates, e.g., morphine an oxycodone	Need for better options to currently available dosage forms Current lack of oral dosage forms for pediatric patients
Cancer	Need for personalized doses of oral drug products
HIV	Need for combination products and personalized doses
Organ transplantation	Need for combination products and personalized doses
Tuberculosis	Need for combination products and personalized doses

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.

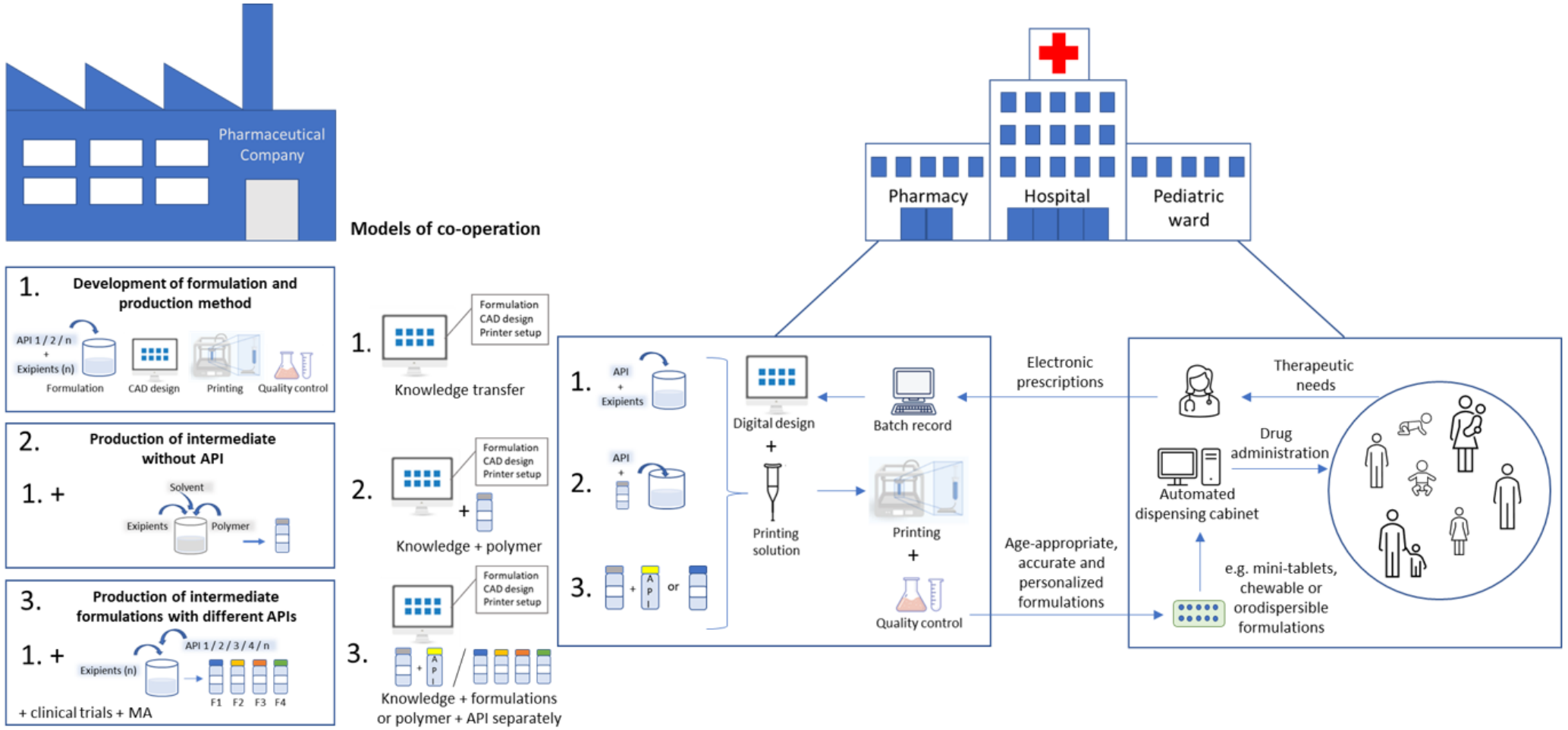
SUMMARY OF KEY RESULTS AND DISCUSSION (STUDY II AND III)

SUBCATEGORY	BENEFITS	CONCERNS	PREREQUISITES	MEASURES
MEDICATION SAFETY	Precise dose	Dose accuracy and quality control	Verification of drug content and dose accuracy	Qualification of equipment (OQ, PQ) Quality control prior delivery
	Imprinting identification directly onto dosage form	Identification of dosage units at hospital wards	Visually different dosage units Identification information	Unit dose packaging Barcode in label Barcode medication administration
	Stability	Shelf-life and storage conditions	Storage in room temperature	Blister packaging Stability studies
DRUG ADMINISTRATION	Personalized doses and formulations	Size of formulation	Small size	Design of formulation according to patient needs
	Ease of drug administration	Administration through feeding tubes	Possibility to dissolve or disperse formulation No blockage of feeding tubes	Formulation development Verification of dose recovery from enteral feeding tubes
PRODUCTION AND DELIVERY ON-DEMAND	Delivery of new products if patient's dose is changed	Length of production time	Process lead times must meet customer needs	Process optimization • prefabricated ink/substrate • printing time • drying time
COSTS	Cost savings	Increased production costs	Cost-efficiency	Cost analysis

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



ORIGINAL PUBLICATIONS

- 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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