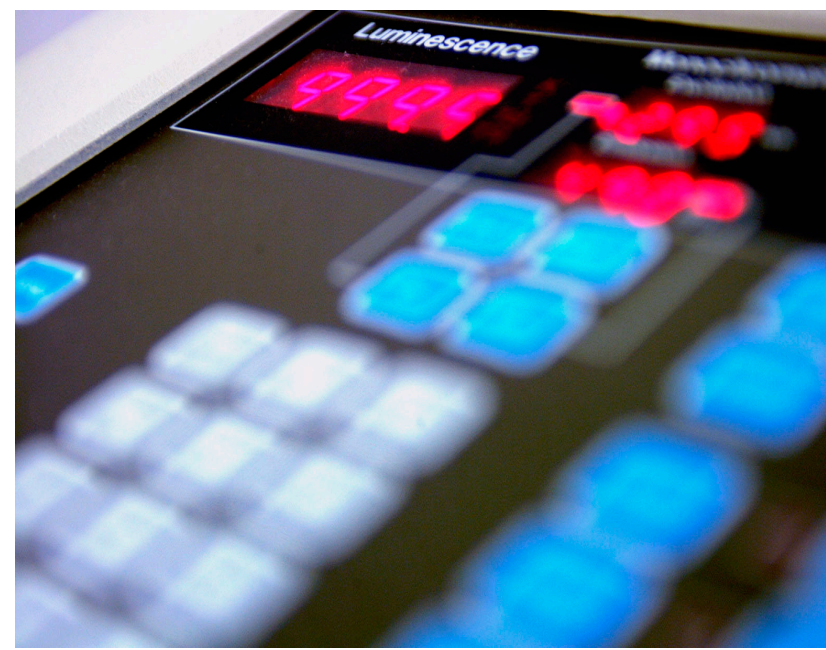




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HOSPITAL



Dr. Torsten Hoppe-Tichy

Printing Drugs

The „Why“ and „How“ from
the perspective of a hospital
pharmacist

Conflict of Interest

THT works in a project around 2D/3D-Printing together with

→ Department of Clinical Pharmacology and
Pharmacoepidemiology, Heidelberg University Hospital, Germany

→ DiHeSys - Digital Health Systems GmbH, Munich, Germany

→ Gen-Plus GmbH, Munich, Germany

without any financial funding or support

Questions

After attending this seminar participants should be able to answer the following questions

Q1: What are the advantages of „Printing Medicines“?

Q2: What is one of the biggest challenge of printing on orodispersible films?

Q3: What are the patient populations with a possible unmet need regarding printed medicines?



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First at all ...

..... this is about 2D-printing!

But, for heavens sake, why shall we print drugs?

Some thoughts on automating

Why is there a need to print drugs?

Is this unmet need the same in any patient group?

The local level approach, perspective Heidelberg University Hospital (UKHD)

How?

Project planing at UKHD



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1st Problem^{DE} (only???)

Small Scale Production in Hospitals^[DE]

drug production in German hospital pharmacies

because

no drug in the market (wrong dose, route of application)

e.g. child care, „ready-to-administer“ syringes

produced from licensed proprietary medicinal products available in the market (→ reworking)

drug too expensive or drug shortages

e.g. rare diseases

produced from „cheap“ raw substances if available in the market

Small-Scale Production in Hospitals^[DE]

„extemporaneous formulation“

individual production for a single patient

e.g. special dose for children → capsules, solutions

„real“ small-scale production

batch production for a patient group

e.g. drug not available or not „ready-to-administer“

Why is this a problem?

Why is this a problem?

The biggest challenges for health systems in the near future

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→ financing

Why is this a problem?

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→ financing

→ staffing/staff recruitment

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👉 *Automating should take place wherever possible!*

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cytotoxic reconstitution, TPN (compounding robots), logistics (unit-dose, picking robots), extemporaneous formulations (2D/3D-printing),



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2nd Problem

Problems in Special Patient Groups

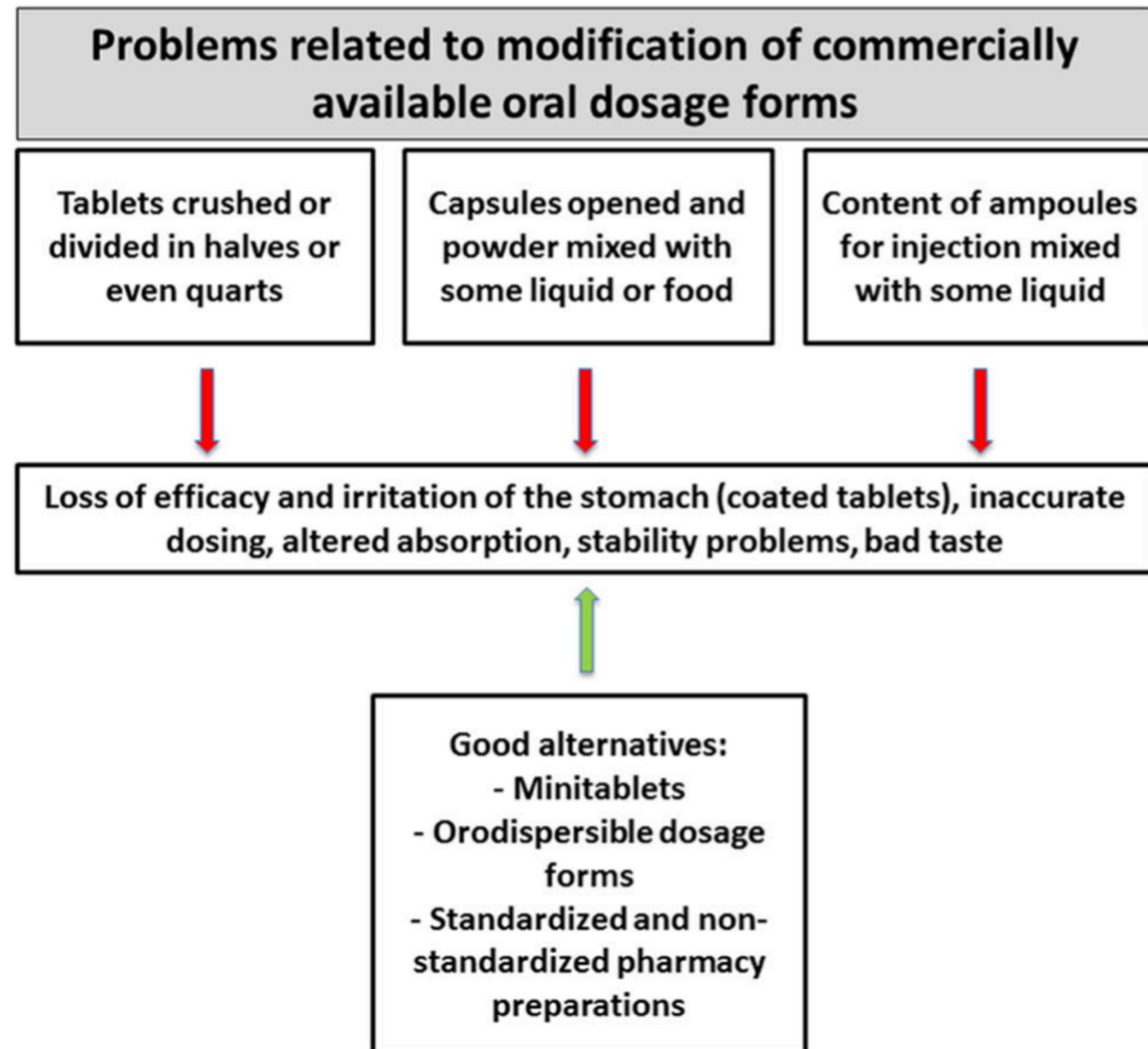
Children

dose of commercial available drugs often has to be adapted

problems with swallowing tablets or capsules

problems with taste of solutions

no data on stability when mixed with food (baby food/mash)



Special Doses for Children → Capsules, Solutions

ADKA's Special Interest Group on Pediatrics names 51 active ingredients which are used in extemporaneous formulations

Wishlists exist in different settings

Reasons are not only „wrong dose“ but also

„bad taste“

„problems with swallowing of tablets and capsules“

→ 11.000 capsules/y

→ 1.500 bottles with liquid formulations/y

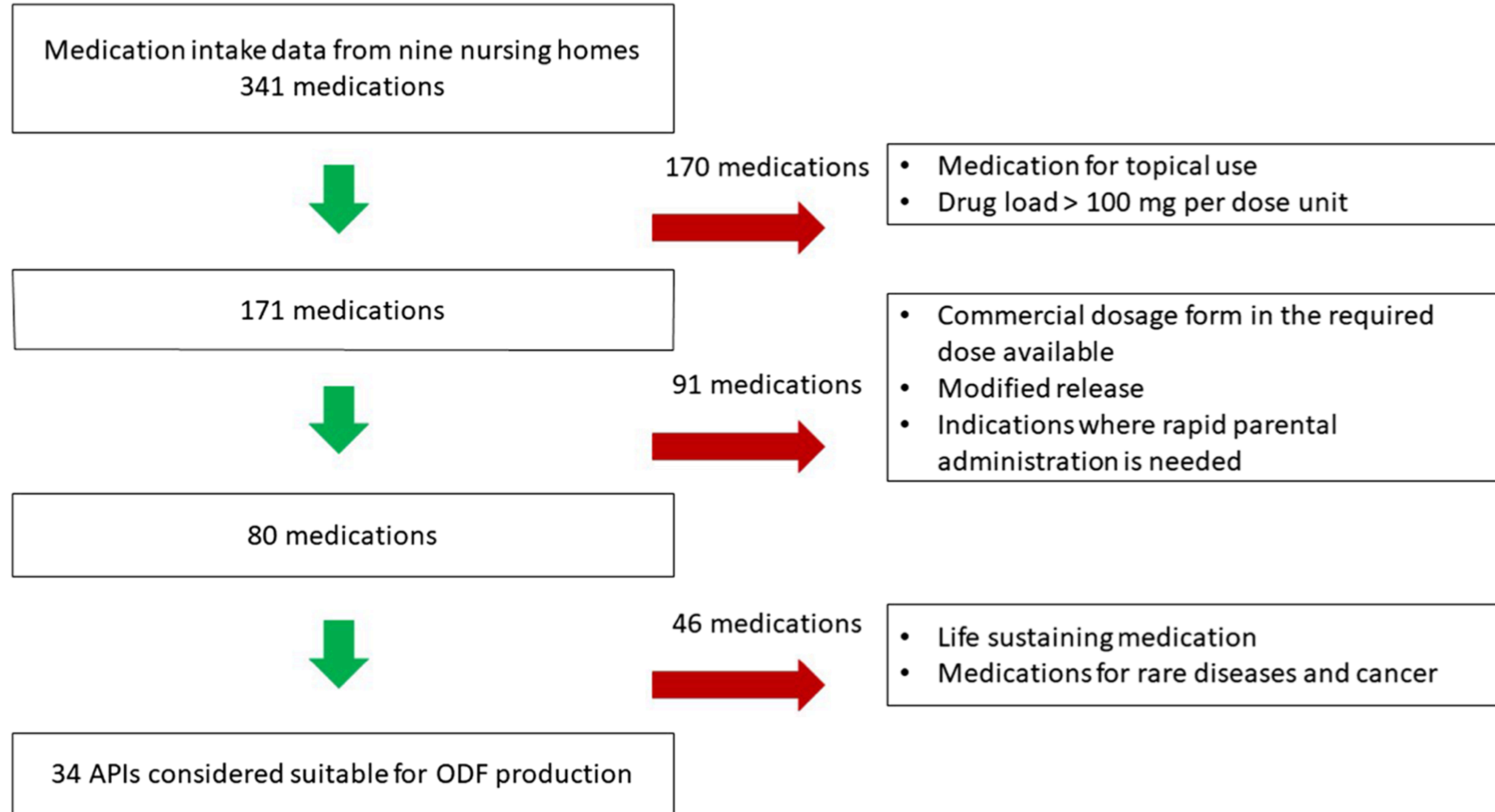
UKHD

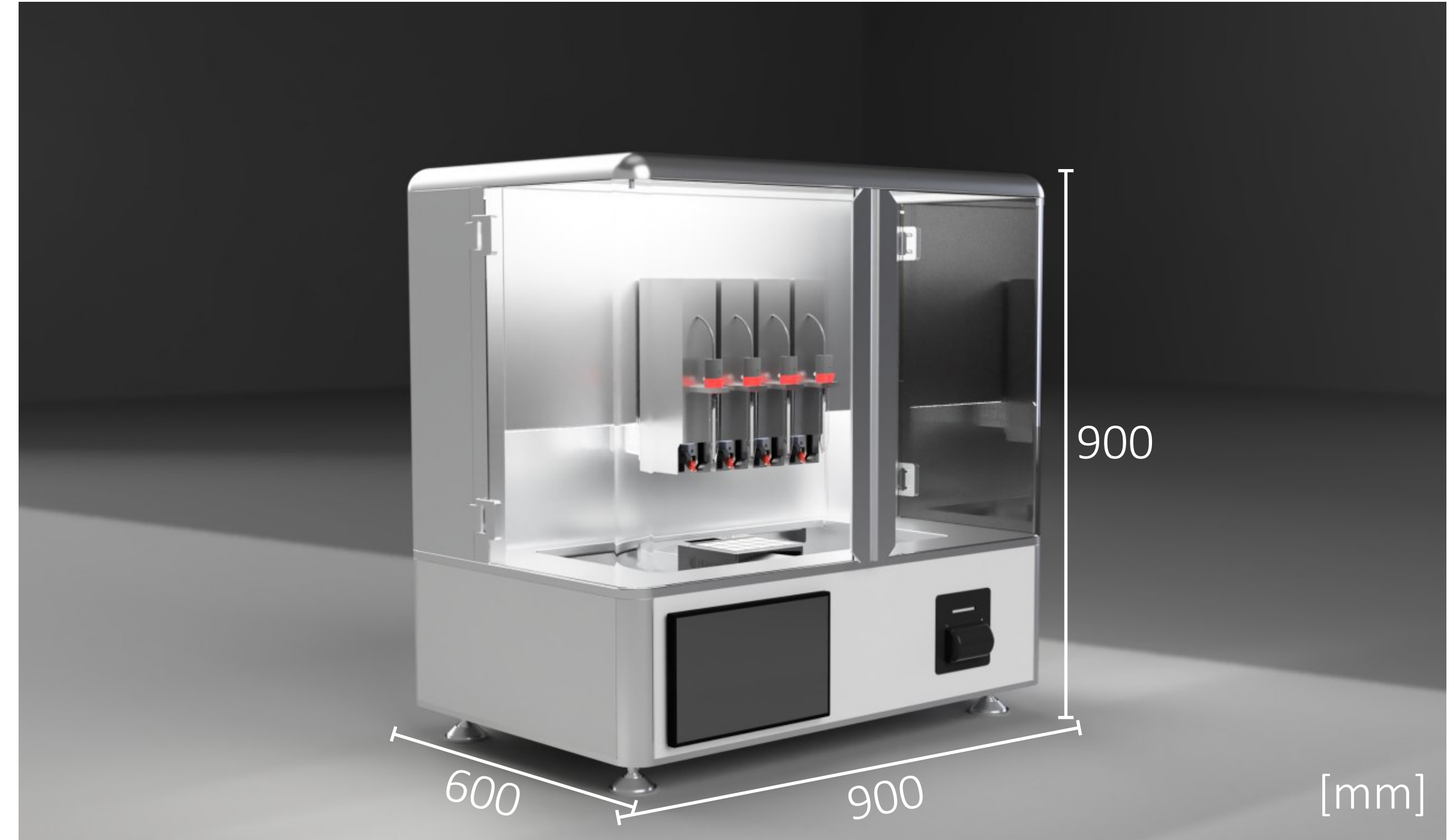
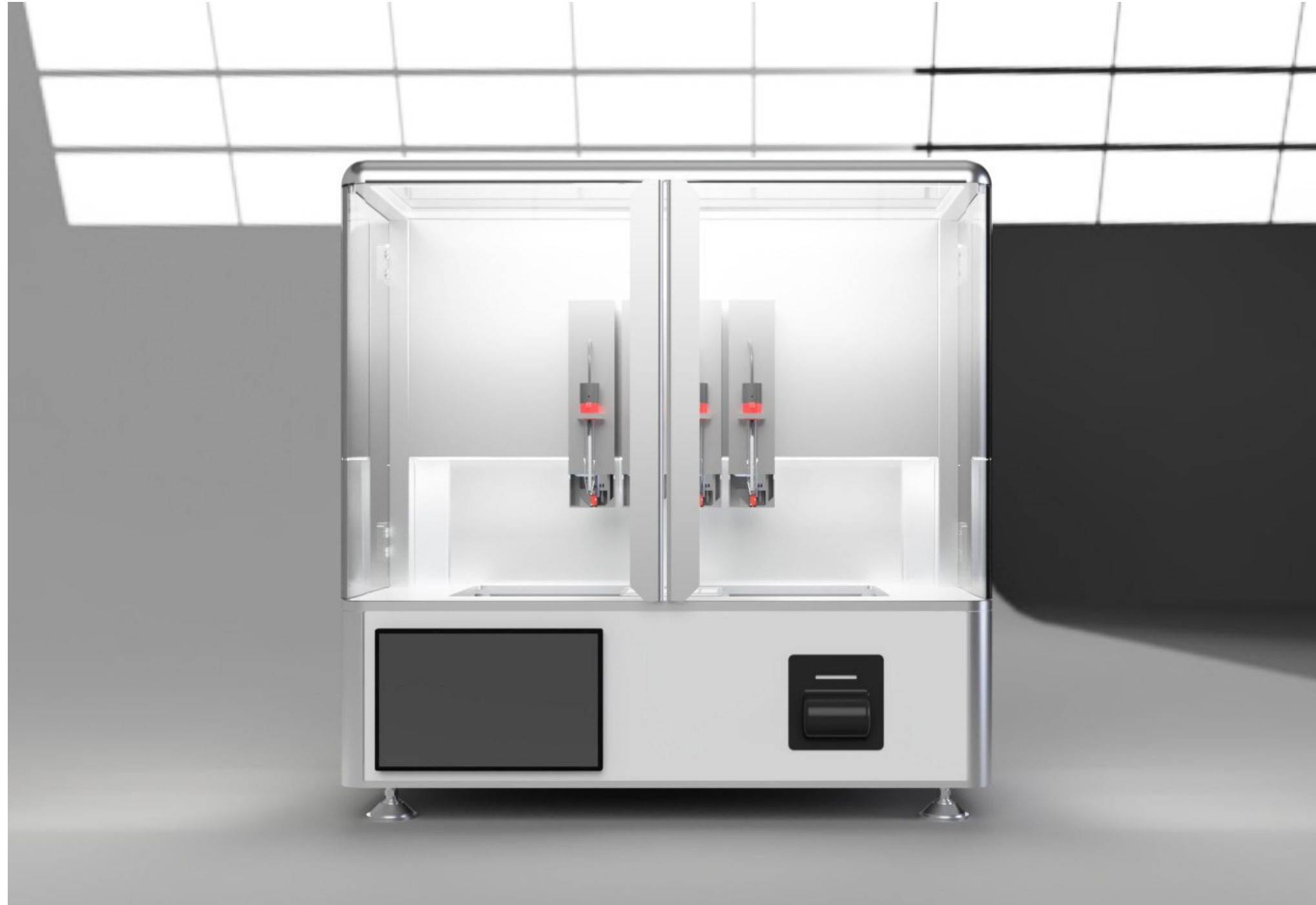
Nr.	Wirkstoff	Formulierung	Indikation	Quelle	Konzentration	Hersteller	Formulierung	Konzentration	Indikation	Quelle
1	Spironolacton	Suspension	Suspension	2001 / Nr.2	2 + 2,5 + 25 mg/ml	stabilis.org	Soft (10 mg/ml)	2,5-10 mg/ml	ab Neonaten: initial 0,25-0,5 mg/kg alle 4-8h - max. 2 mg/kg alle 6 h	Bremen
2	Sildenafil	Suspension	Suspension		Kompatibilitätstabelle 2,5 mg/ml	stabilis.org	Soft (10 mg/ml)	2,5-10 mg/ml	Neonaten: 0,25-0,5mg/kg 3x tgl. bis 2mg/kg 3x tgl.	
3	Propranolol(hydrochlorid)	Lösung	Lösung		Kompatibilitätstabelle 0,5 + 1 + 5 mg/ml	stabilis.org	Lösung	1 mg/ml, 3,75 mg/ml und 5 mg/ml	1 Monat-12 Jahre: bis 5mg/kg tgl.	
4	Captopril	Lösung	Lösung		Kompatibilitätstabelle 10 mg/ml	stabilis.org	Lösung	1 mg/ml	Neonaten: 0,5-1 mg/kg	Essen
5	Coffein(citrat)	Lösung	Lösung		Kompatibilitätstabelle 10 mg/ml	PZ 1992 / Nr.25	Lösung	5 mg/ml, 10 mg/ml, 20 mg/ml	Erhaltungsdosis 5 mg/kg Coffein Base 1x tgl.	Bremen
6	Chloralhydrat	Lösung	Lösung		Kompatibilitätstabelle 10 mg/ml	Lösung FNA	FAM-Import	70 mg/ml und 100 mg/ml	Neonaten: 30-50 mg/kg bis zu 100 mg/kg	
7	Hydrochlorothiazid	Suspension	Suspension	2001 / Nr.2	2,5 mg/ml	stabilis.org	Lösung	1 mg/ml	1. Monat-12 Jahre: 30-50 mg/kg bis 100 mg/kg	Bremen
8	Clonidin(hydrochlorid)	Lösung	Lösung	2016 / Nr. 6	Lösung 0,1 mg/ml	stabilis.org	Lösung	0,5 µg	2-18 Jahre: 0,5-1 µg/kg bis zu 25 µg/kg tgl.	Dresden, H
9	Metoprolol(tartrat)	Lösung	Lösung + Suspension	2010 / Nr. 6	Lösung 5 mg/ml	stabilis.org	Lösung	1 mg ???	1 Mon. - 12 Jahre: 1 mg/kg 2x tgl. - bis 8 mg/kg verteilt auf 2-4 Dosen	Erf
10	Melatonin	Lösung	Lösung + Suspension	2008 / Nr. 1	Lösung 2 mg/ml	stabilis.org	Lösung	1 mg	2-3 mg initial Steigerung auf 4-6 mg möglich max. 10 mg	Regen
11	Enalapril(maleat)	Lösung	Lösung		Kompatibilitätstabelle 1 mg/ml	Lösung FNA	Lösung	1 mg/ml	Neonaten: 10-50 µg/kg	
12	Natriumbenzoat	Lösung	Lösung		Lösung	Lösung	Lösung	1 mg/ml	1.Monat-12 Jahre: 100 µg/kg in 1-2 Dosen	
13	Lisinopril	Lösung	Lösung		Kompatibilitätstabelle 1 mg/ml	Lösung	Lösung	1 mg/ml	ab Neonaten: initial 50-150mg/kg 3-4x tgl.	
14	Amlodipin(besilat)	Lösung	Lösung		Kompatibilitätstabelle 1 mg/ml	Lösung	Lösung	0,5 mg	6-12 Jahre: 70 mg/kg (max. 5 mg abs.) bis zu 600 µg/kg	
15	Omeprazol	Lösung	Lösung		Kompatibilitätstabelle 2+5 mg/ml	extemporaneous formulations for pediatric use	Lösung	2 mg/ml	Neonaten: 1x tgl. 0,7mg/kg (bis 2,8mg/kg)	
16	Carvedilol	Lösung	Lösung		Kompatibilitätstabelle 1+5 mg/ml	Suspension Farmacia Hospitalia2010; 34 (6)	Lösung	1 mg/ml	2-18 Jahre: initial 50 µg/kg bis zu 350 µg/kg (max. 25 mg abs.) 2xtgl.	
17	Tacrolimus	Lösung	Lösung		Kompatibilitätstabelle 0,5 + 1 mg/ml	stabilis.org, extemporaneous formulations for pediatric geriatric and special needs patients	Modigraf-Granulat	1 mg	meist: 0,15mg/kg 2x tgl.	
18	Hydrocortison	Lösung	Lösung		Kompatibilitätstabelle 1 mg/ml	Suspension Int. J. Pharm. Compound. 8 (2004)	Lösung	1 mg	Neonaten: 9-15 mg/m3	
19	Levothyroxin(natrium)	Lösung	Lösung		Lösung	Lösung	Lösung	5 µg	1.Monat-18 Jahre: 8-15 mg/m3	
20	Flecainid(acetat)	Lösung	Lösung		Kompatibilitätstabelle 20 mg/ml	Lösung	Lösung	25 µg/ml	Neonaten: 10-15 µg/kg bis max. 50 mg tgl.	
21	Midazolam(hydrochlorid)	Lösung	Lösung		Kompatibilitätstabelle 1 mg/ml	Lösung	Lösung	1 mg/ml	1.Monat-2 Jahre: 5 µg/kg bis zu 75 µg	
22	Morphin(hydrochlorid)	Lösung	Lösung		Fagron - Compounding matters 20 mg/ml	Lösung	Lösung	25 µg/ml	2-12 Jahre: 25-100 µg 12-18 Jahre 25-200 µg	
23	Sotalol	Lösung	Lösung	2014 / Nr. 5	Lösung 5mg/ml	stabilis.org	Import - FAM	2-20 mg/ml	Neonaten: 2 mg/kg 2-3xtgl.	
24	Metronidazol	Lösung	Lösung		Kompatibilitätstabelle 80 mg/ml	stabilis.org	Import - FAM	25 mg/ml	1.Monat-12 Jahre: 2 mg/kg 2-3 x tgl. max. 8 mg/kg tgl.	
25	Phenobarbital	Lösung, Fetteulsion	Lösung		Kompatibilitätstabelle 9 mg/ml	stabilis.org	Import - FAM	9 mg/ml und 10 mg/ml	1 Mon. - 12 Jahre: initial 1-1,5 mg/kg 2x tgl. - übliche Dosis 2,5-4mg/kg gesteigert	
26	Theophyllin	Lösung	Lösung		Fagron - Compounding matters 10 mg/ml	stabilis.org	Import - FAM	10 mg/ml	12-18J: 60-180 mg	
27	Valganciclovir	Lösung	Lösung		Fagron - Compounding matters 30-60 mg/ml	stabilis.org	Import - FAM	50 mg/ml	6-12 Monate: 12 mg/kg alle 12 h	
28	Acetazolamid	Lösung	Lösung		Kompatibilitätstabelle 25 mg/ml	Suspension Pediatric Drug Formulations, Fourth Edition	Lösung	25 mg/ml	1 Mon.-12 Jahre: initial 1-1,5 mg/kg 2x tgl. - übliche Dosis 2,5-4mg/kg gesteigert	
29	Azathioprin	Lösung	Lösung		Fagron - Compounding matters 50 mg/ml	Suspension Pediatric Drug Formulations, Sixth Edition	Lösung	50 mg/ml	1 Monat-12 Jahre: 2,5 mg/kg bis 5-7 mg/kg tgl.	Dresden, Tübingen
30	Colecaciferol	Lösung	Lösung		Kompatibilitätstabelle 50.000 IE/ml	Lösung	Lösung	40.000 IE / ml	1.Monat bis 2 Jahre: 1 mg/kg bis max. 3 mg/kg	
31	Clenbuterol	Lösung	Lösung		Lösung	Lösung	Lösung	5 µg/ml, 10 µg ml	2-18 Jahre: 2 mg/kg	
32	Clopidogrel	Lösung	Lösung		Fagron - Compounding matters 5 mg/ml	Lösung	Lösung	5 mg/ml	Neonaten: 400 IE/tgl.	
33	Colistin	Lösung	Lösung		Lösung	Lösung	Lösung	5 mg/ml	1. Monat- 18 Jahre: 400-600 IE tgl.	

Trametinib	PaedOnko
Dabrafenib	PaedOnko
Risperidon	Psych
Quetiapin	Psych
Haloperidol	Psych
„Tinibe“	Thorax
ASS	Paed allgemein
Clopidogrel	Paed allgemein
Ramipril	Paed allgemein
Penicillin	
Corticosteroide	Paed allgemein



Environment: Nursing Home





possible problem-solving model



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What does it mean to implement
such a system in hospital pharmacy?

„What does it mean to implement such a system in hospital pharmacy?“

→ you need partners

development, implementation, research, clinical study,

→ you should have an innovation-friendly environment

→ you need the money

→ you have to find enthusiastic pharmacists in your department

→ your team should have enough knowledge around drug production issues

Implementation/Research

Decision → Which drug should be studied?

Analytics → HPLC method

Production of ink

Solvent?

Stability testing for selected ink (→ stress tests)

Substrate development (→ Which kind of orodispersible film¹?)

Compatibility/Stability testing of ink/solvent on ODF

Adaption → ink, thickness of ODF, printing process, temperature

¹Orodispersible Film: ODF

Questions before you start

Solubility

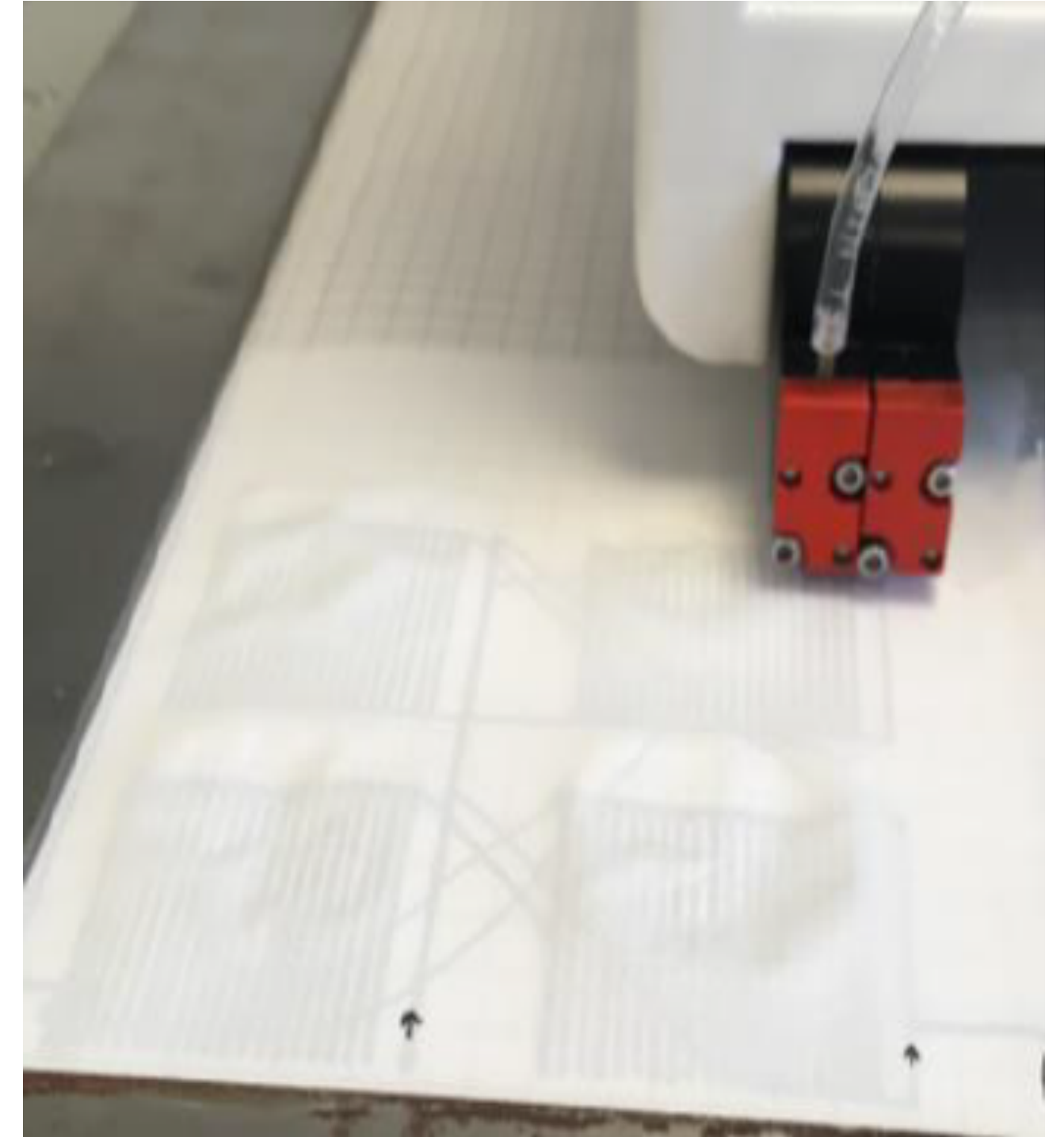
Is the drug soluble in an „printing-appropriate“ solvent?

Is the drug stable in the ink (solvent)?

Is the ink printable?

Will the concentration of the ink be high enough to get a dose printed?

Is the ink (solvent) compatible with the ODF chosen?



Questions before you start

Orodispersible films (ODF)

which is the right formulation of the ODF

(physical) stability

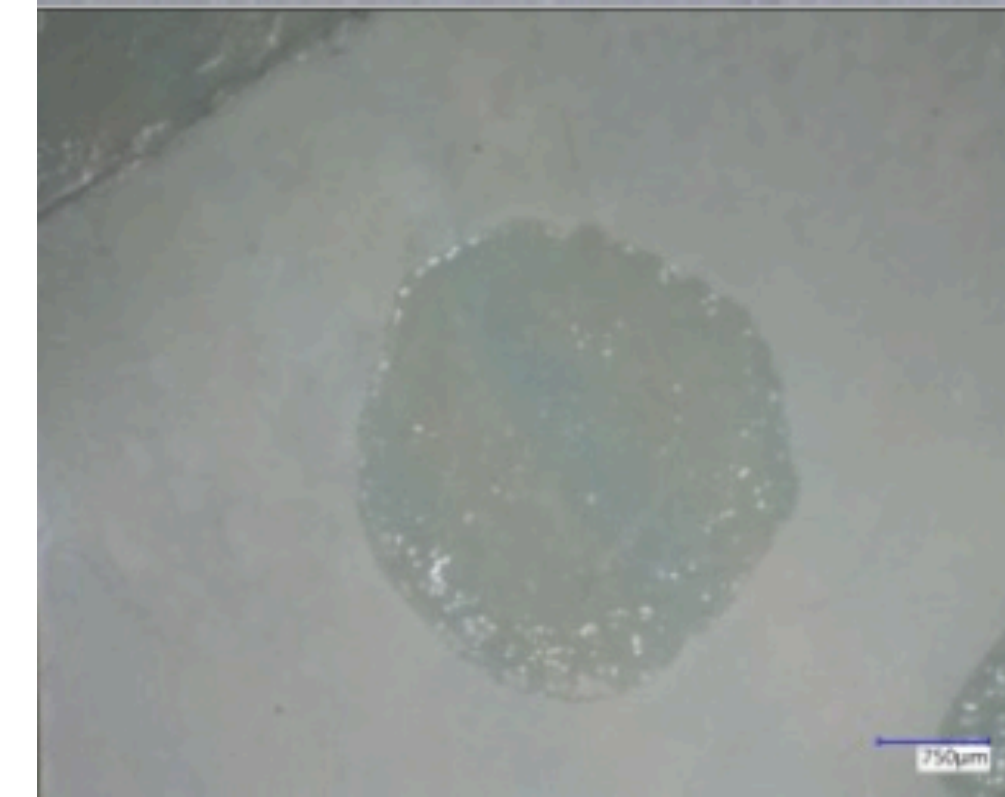
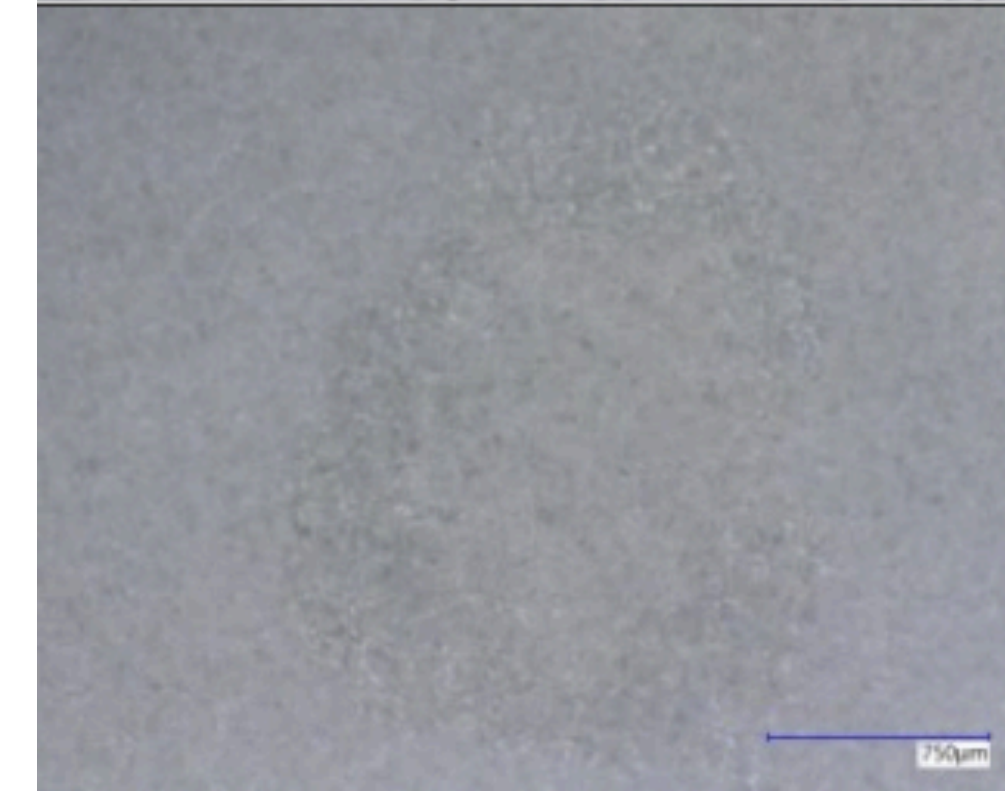
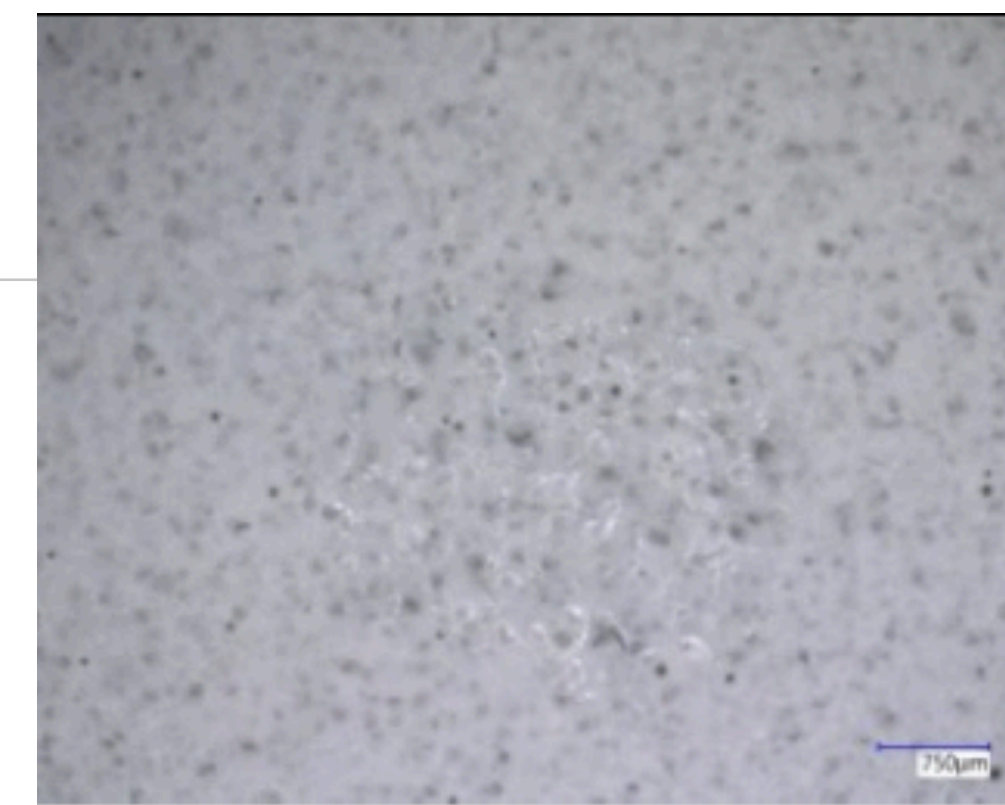
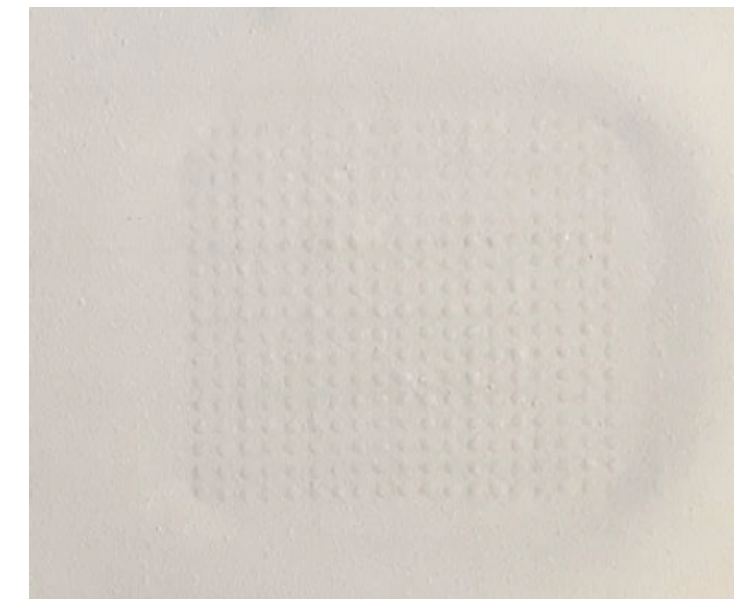
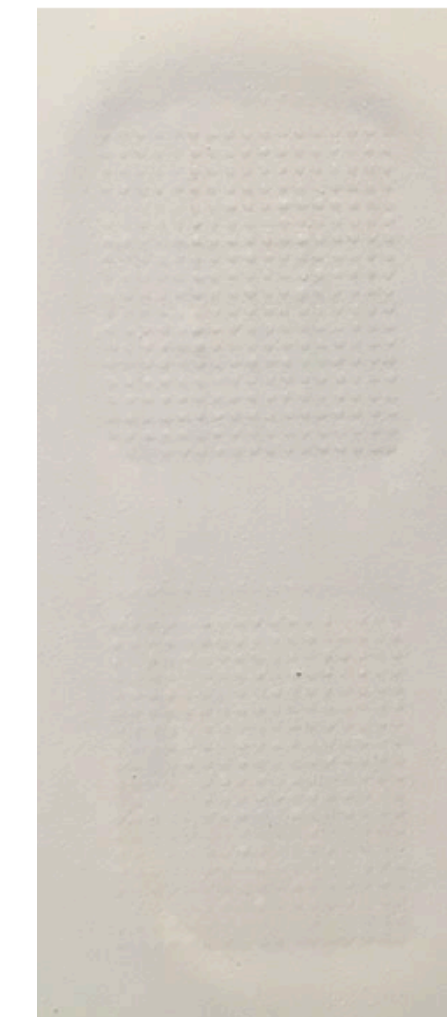
disintegration time

release of drug

carrying capacity („ink“)

storage conditions

compatibility with ink



Our Wishlist

extemporaneous production of ink should be possible in hospital pharmacy

changing ink should be easy

easy cleaning procedure of printhead is a prerequisite

→ cross contamination protocols

different ODFs should be easily available (like empty capsules)

easy and cost-effective packaging of printed ODFs should be developed

Conclusion

In our center children with the need for individualized oral dosages are the target population

Geriatric patients with polypharmacy¹ might be another patient population

2D-Printing on ODF is the preferred method at UKHD

¹Polypharmacy is defined by the World Health Organisation as "the administration of many drugs at the same time or the administration of an excessive number of drugs"