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Dr. Torsten Hoppe-Tichy

Printing medicines in the hospital pharmacy – what should we pay attention to?

GSASA GA & Congress 2024, Basel

UK HD

Conflict of Interest

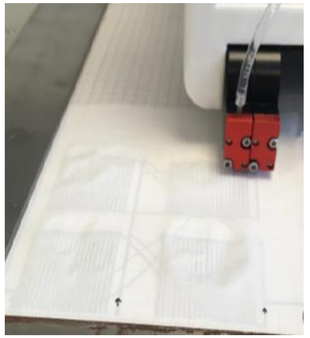
Research cooperation with DiHeSys/GenPlus and with CurifyLabs

„Owner“ of different printers

DiHeSys: FlexDose-Printer

CurifyLabs: Pharma Printer 1

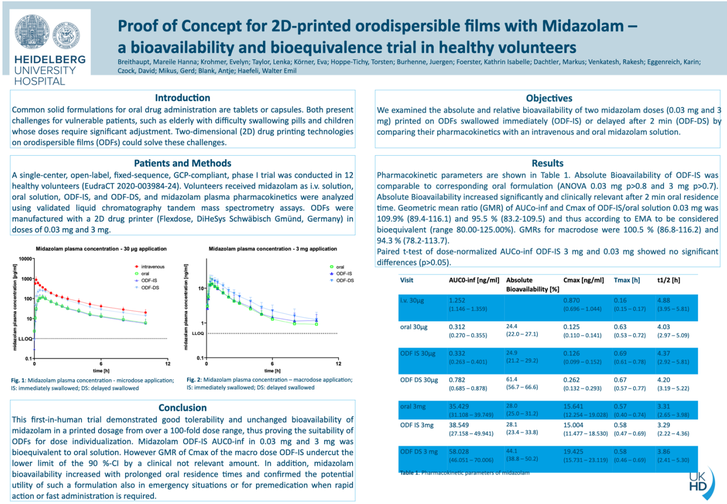
FabRx: M3DIMAKER^2



04.03.2021
ts-sk

ZUSTIMMENDE BEWERTUNG

EudraCT-Nr.:	2020-003984-24
Prüfplan-Code:	K723
Verfahrens-Nr.:	PB-0270
Titel:	Evaluation of the perpetrator characteristics of metamizole (dipyrone) on the activity of CYP3A4 in healthy volunteers by using a new orodispersible film formulation of midazolam
Sponsor:	Ruprecht-Karls University Heidelberg, Medical Faculty, University Hospital
Antragsteller:	University Hospital Heidelberg
Prüfer:	Prof. Dr. med. Walter E. Haefeli, Heidelberg
Unser Zeichen:	AFmo-012/2021 (Bitte stets angeben)



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Proof of Concept for 2D-printed orodispersible films with Midazolam – a bioavailability and bioequivalence trial in healthy volunteers

Breithaupt, Marelle Hanna; Krohmer, Evelyn; Taylor, Lenka; Körner, Eva; Hoppe-Tichy, Torsten; Burhenne, Juergen; Foerster, Kathrin Isabelle; Dachtler, Markus; Venkatesh, Rakesh; Eggenreich, Karin; Cook, David; Mikus, Gerd; Blank, Antje; Haefeli, Walter Emil

Introduction

Common solid formulations for oral drug administration are tablets or capsules. Both present challenges for vulnerable patients, such as elderly with difficulty swallowing pills and children whose doses require significant adjustment. Two-dimensional (2D) drug printing technologies on orodispersible films (ODFs) could solve these challenges.

Patients and Methods

A single-center, open-label, fixed-sequence, GCP-compliant, phase I trial was conducted in 12 healthy volunteers (EudraCT 2020-003984-24). Volunteers received midazolam as i.v. solution, oral solution, ODF-IS, and ODF-DS, and midazolam plasma pharmacokinetics were analyzed using validated liquid chromatography tandem mass spectrometry assays. ODFs were manufactured with a 2D drug printer (Flexdose, DiHeSys Schwäbisch Gmünd, Germany) in doses of 0.03 mg and 3 mg.

Objectives

We examined the absolute and relative bioavailability of two midazolam doses (0.03 mg and 3 mg) printed on ODFs swallowed immediately (ODF-IS) or delayed after 2 min (ODF-DS) by comparing their pharmacokinetics with an intravenous and oral midazolam solution.

Results

Pharmacokinetic parameters are shown in Table 1. Absolute Bioavailability of ODF-IS was comparable to corresponding oral formulation (ANOVA 0.03 mg p>0.8 and 3 mg p>0.7). Absolute Bioavailability increased significantly and clinically relevant after 2 min oral residence time. Geometric mean ratio (GMR) of AUCo-inf and Cmax of ODF-IS/oral solution 0.03 mg was 109.9% (89.4-116.1) and 95.5 % (83.2-109.5) and thus according to EMA to be considered bioequivalent (range 80.00-125.00%). GMRs for macrodose were 100.5 % (86.8-116.2) and 94.3 % (78.2-113.7).
Paired t-test of dose-normalized AUCo-inf ODF-IS 3 mg and 0.03 mg showed no significant differences (p>0.05).

Fig. 1: Midazolam plasma concentration – microdose application; IS: immediately swallowed; DS: delayed swallowed

Fig. 2: Midazolam plasma concentration – macrodose application; IS: immediately swallowed; DS: delayed swallowed

Visit	AUCO-inf [ng/ml]	Absolute Bioavailability [%]	Cmax [ng/ml]	Tmax [h]	t1/2 [h]
i.v. 30µg	1.252 (1.146 – 1.359)		0.870 (0.696 – 1.044)	0.16 (0.15 – 0.17)	4.88 (3.95 – 5.81)
oral 30µg	0.312 (0.270 – 0.355)	24.4 (22.0 – 27.1)	0.125 (0.110 – 0.141)	0.63 (0.53 – 0.72)	4.03 (2.97 – 5.09)
ODF IS 30µg	0.332 (0.263 – 0.401)	24.9 (21.2 – 29.2)	0.126 (0.099 – 0.152)	0.69 (0.61 – 0.78)	4.37 (2.92 – 5.81)
ODF DS 30µg	0.782 (0.685 – 0.878)	61.4 (56.7 – 66.6)	0.262 (0.132 – 0.293)	0.67 (0.57 – 0.77)	4.20 (3.19 – 5.22)
oral 3mg	35.429 (31.549 – 39.749)	28.0 (25.2 – 31.2)	15.641 (13.254 – 18.028)	0.57 (0.50 – 0.74)	3.31 (2.53 – 4.09)
ODF IS 3mg	38.549 (27.158 – 49.941)	28.1 (23.4 – 33.8)	15.004 (11.477 – 18.530)	0.58 (0.47 – 0.69)	3.29 (2.22 – 4.36)
ODF DS 3 mg	58.028 (46.051 – 70.006)	44.1 (38.8 – 50.2)	19.425 (15.733 – 23.119)	0.58 (0.46 – 0.69)	3.86 (2.41 – 5.30)

Table 1: Pharmacokinetic parameters of midazolam

Conclusion

This first-in-human trial demonstrated good tolerability and unchanged bioavailability of midazolam in a printed dosage from over a 100-fold dose range, thus proving the suitability of ODFs for dose individualization. Midazolam ODF-IS AUC0-inf in 0.03 mg and 3 mg was bioequivalent to oral solution. However GMR of Cmax of the macro dose ODF-IS undercut the lower limit of the 90 %-CI by a clinical not relevant amount. In addition, midazolam bioavailability increased with prolonged oral residence times and confirmed the potential utility of such a formulation also in emergency situations or for premedication when rapid action or fast administration is required.

Semi Solid Extrusion (SSE)

Fused Deposition Modelling (FDM)

Direct Powder Extrusion (DPE)

Own pictures or from homepages of companies

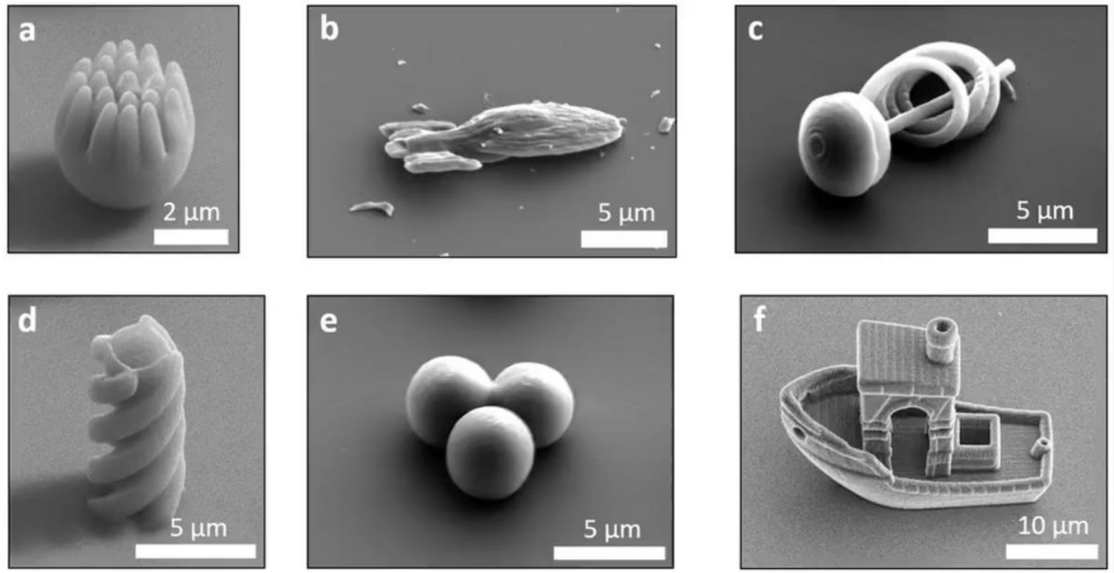
Agenda

Why is printing of medicines an interesting approach for hospital pharmacies?

How do we do it?

What are the „no-goes“ for us?

When will we have a routine printing production at UKHDs Pharmacy Department?



Doherty RP et al. Catalytically propelled 3D printed colloidal microswimmers .SoftMatter 2020;16:10463–10469 [*3D printing by two-photon polymerisation*]

Fig. 2. Chewable printlets in different flavours/colour and doses. From left to right: Lemon-yellow, coconut-black, banana-light green, orange-orange, raspberry-light blue, strawberry-red. From top to bottom: 50 mg, 100 mg, 150 mg and 200 mg. Units are cm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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why

UK
HD

Mission Statement (UKHD, automatization)

The biggest challenges for health systems in the near future

➔ financing

➔ staffing/staff recruitment

☞ *Automating should take place wherever possible!*

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

one-size-fits-all or personalized therapy

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one capsule for everyone …

dose adjustment, stratified Tx, Biomarker, personalized, … …

severe ADR

insufficient or no effect (Non-Responder)

good effect (Responder)

UK HD

Patient groups

- Paediatrics
  - individualized doses, doses for children not available in the market
    - capsules [content pored on (hot) food] or solutions (taste!)
- Geriatrics
  - many different drugs, problems with swallowing

Patient groups

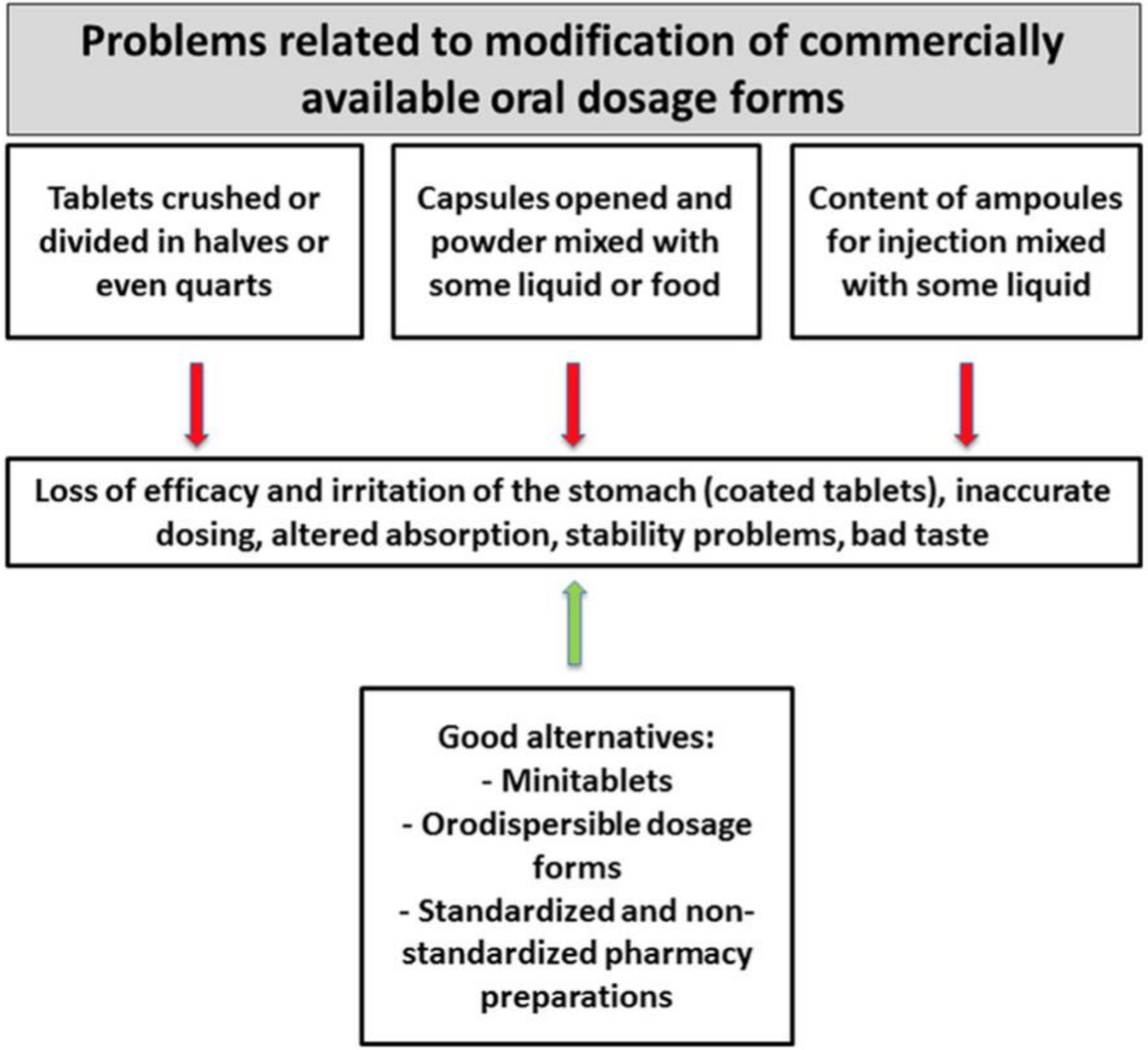
Children

dose adjustment needed

problems with swallowing of capsules and tablets

problems with taste (e.g. oral solutions)

lack of stability data for mixing the medicine with food (e.g. pablum)



Visser JC, Woerdenbag HJ, Hanff LM, Frijlink HW. Personalized Medicine in Pediatrics: The Clinical Potential of Orodispersible Films. AAPS Pharm Sci Tech 2017;18(2):267

Problem solving: Orodispersible Films (ODF)?

Figure 1. (**A**) EXT drug-loaded ODF imprinted with a QR code containing information about the dosage form and (**B**) the same EXT ODF rolled up to visualize the flexibility of the film. (**C**) IJP drug-loaded ODF with a printed QR code and (**D**) the flexible ODF is subsequently coiled up for illustrative purposes.

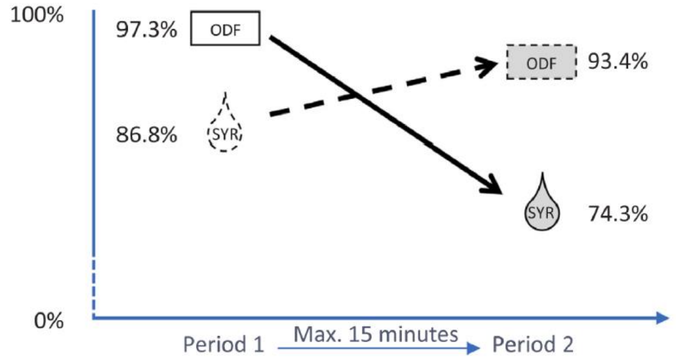


Fig. 3. Acceptability of an orodispersible film compared to syrup in neonates and infants in all age groups in periods 1 and 2. Results of subjects receiving the ODF in the first study period followed by syrup in the subsequent second study period order (solid line) and the reverse treatment order (dashed lines). SYR = syrup. Reprinted from Eur J Pharm Biopharm, 151, Klingmann et al., Acceptability of an orodispersible film compared to syrup in neonates and infants: A randomized controlled trial, [14], Copyright 2020, with permission from Elsevier.

API: warfarin sodium
Strength: 0.1 mg
Patient: Baby Doe
Social security number: 010119A0101
Age: 4 months
Weight: 5.2 kg (21.3.2019)
Indication: anticoagulant
Dose: 0.1 mg ODF in the morning
Treatment duration/re-evaluation: until 30.3.2019
Administration: One 0.1 mg ODF placed on the tongue
Prescribing doctor: Dr. John Doe
Manufacturing unit: HUS Pharmacy
Manufacturing date: 21.3.2019
Expiration date: 21.4.2019
Excipients: purified water, ethanol 94%, HPC EXF, brilliant blue
Storage conditions: store protected from light

Figure 2. Example of the information that could be included in the QR code.

What are we doing now (status quo)?

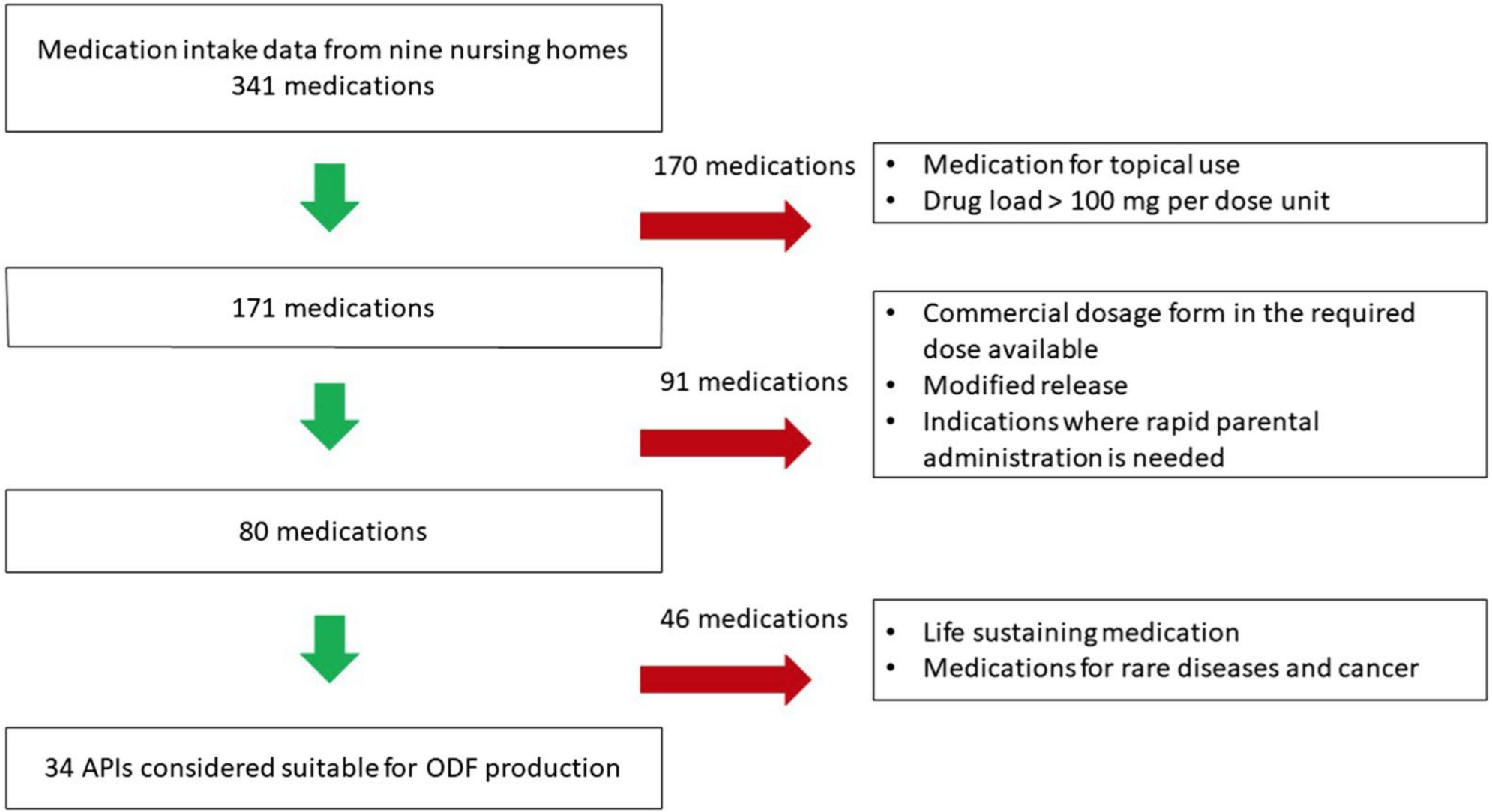
What about drug safety?

How can we mask bad taste?

What about pre-loaded ODF?

Öblom H et al. 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; doi:10.3390/pharmaceutics11070334. Morath B et al. Orodispersible films – Recent developments and new applications in drug delivery and therapy. Biochemical Pharmacology 2022, https://doi.org/10.1016/j.bcp.2022.115036.

Patient groups: geriatric patients



Visser JC, Wibier L, Mekhaeil M, Woerdenbag HJ, Taxis K. Orodispersible films as a personalized dosage form for nursing home residents, an exploratory study. Int J Clin Pharm 2020 Feb 13. doi: 10.1007/s11096-020-00990-w. [Epub ahead of print]

Problem solving: Poly-Pills made by 3D-printers?

Is this also possible when printing on ODFs?

pre-loaded ODF?

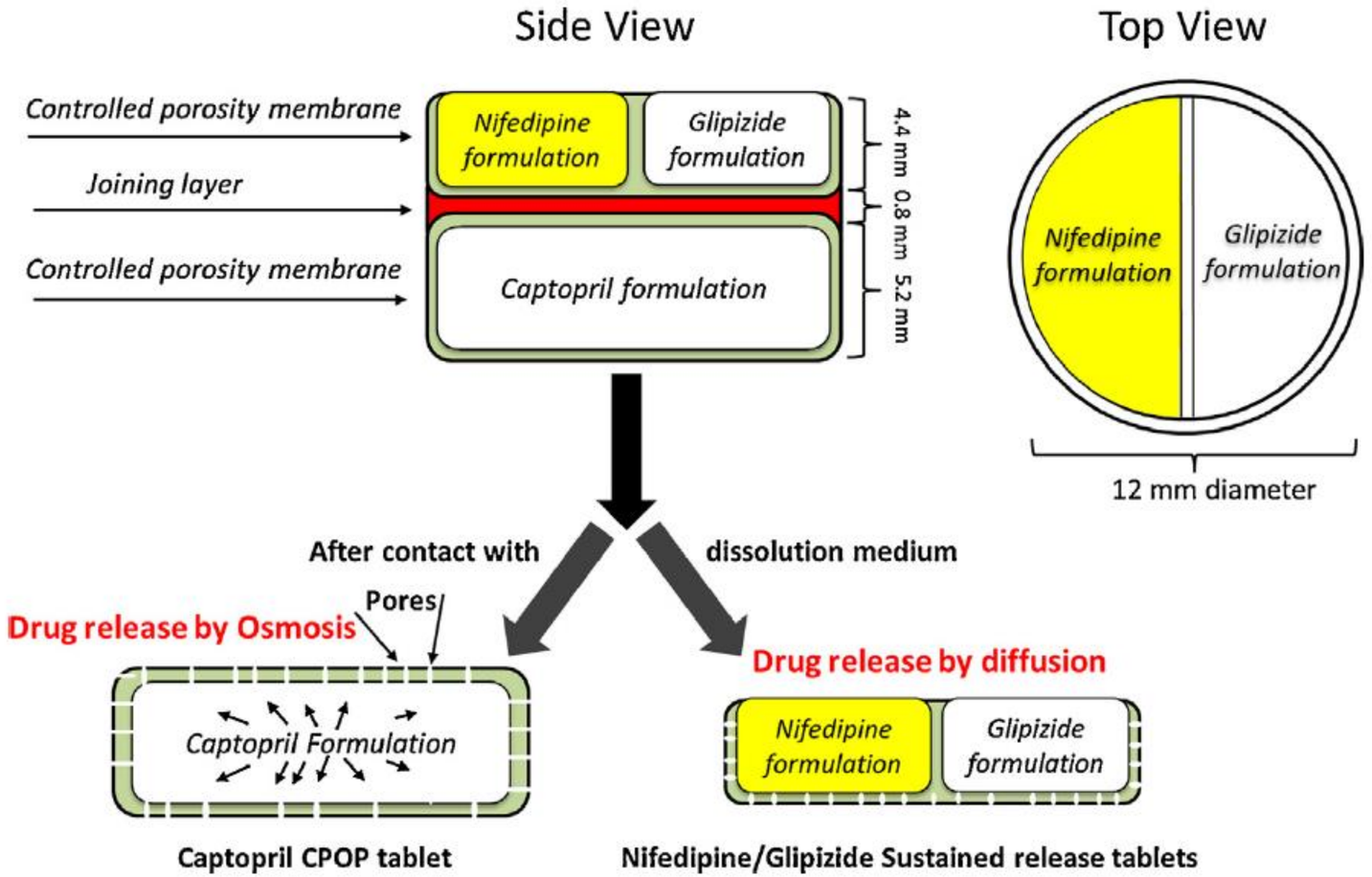


Fig. 1. Schematic structural diagram of captopril osmotic pump and nifedipine and glipizide sustained release tablet.

Khaled SA et al. 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharmaceutics 2015;494:643-50.

what do we need (part I)

flexibility and speed are key

With the help of printers hospital pharmacists must be in a position to fill individual prescriptions quickly and safely

➜ individually produced medicines should reach the ward/patient within 24 hours

process (e.g.): prescription from childcare physician (personalized, individual dosage/application form) ➜ plausibility check by pharmacist

Framework conditions

scientific background, plausibility

cost calculation

facilities, experience, … …

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the role of regulatory bodies

UK
HD

„Small Scale Production“ in hospital pharmacy [DE]

Why …

There is no medicine on the market with the required specification

missing dosage, “wrong” way of application

e.g. children, “ready-to-administer” syringes

➜ approved medicines are being reworked

Available medicines are too expensive or cannot be delivered, e.g. rare diseases

➜ medicines are manufactured from available raw materials in compliance with make-or-buy and the requirements of pharmacy laws (often GMP conditions)

„Small Scale Production“ in hospital pharmacy [DE]

Rezeptur („extemporaneous drug production“)

individual production for single patients

e.g. dosages suitable for children, adjusted dosages in case of organ dysfunction (capsules, solutions)

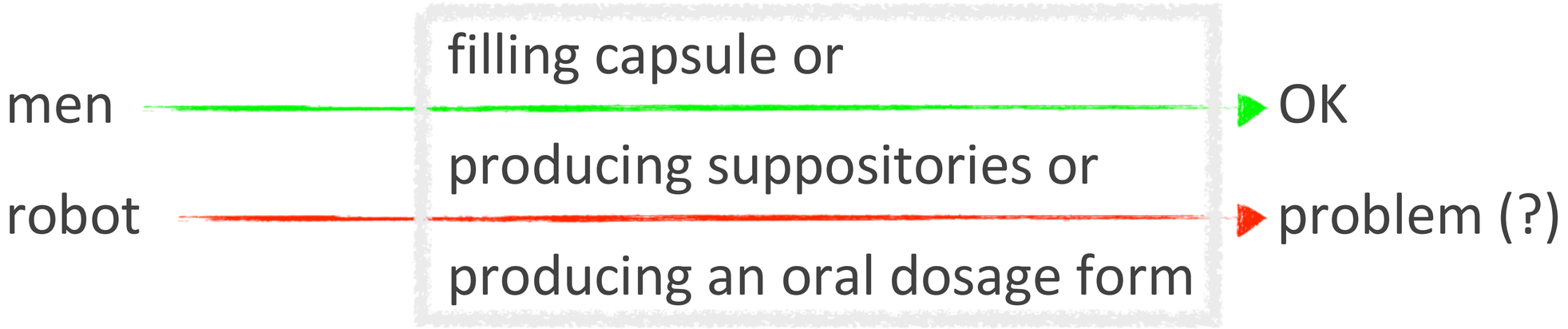
Defektur

batch-production for certain patient groups

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

My personal impression regarding decisions of regulatory boards

Different perspectives on different processes



Other processes

producing loaded orodispersible films vs. printing on orodispersible films

Approach to satisfy regulatory bodies

Is it a printer or a doser?

Weight-controlled dosing into suppository moulds

Weight-controlled dosing into blister moulds resulting in a printlet

In any case → it is a device/an equipment to produce individualized/personalized medicines

→ very small individualized batches (n = daily dose) to make fast adaption (different dose) possible without producing pharmaceutical waste

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what do we need (part II)

UK
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Knowledge …

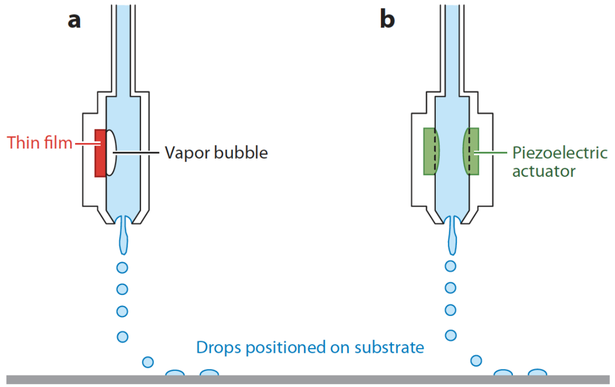


Figure 2

Schematic diagram showing the principles of operation of a drop-on-demand (DOD) inkjet printing system. Drops are ejected by a pressure pulse generated in a fluid-filled cavity behind the printing orifice. This pressure pulse can be generated by (*a*) a vapor pocket or bubble generated by a thin-film heater (thermal inkjet) or (*b*) a mechanical actuation, e.g., from a piezoelectric transducer (piezoelectric inkjet).

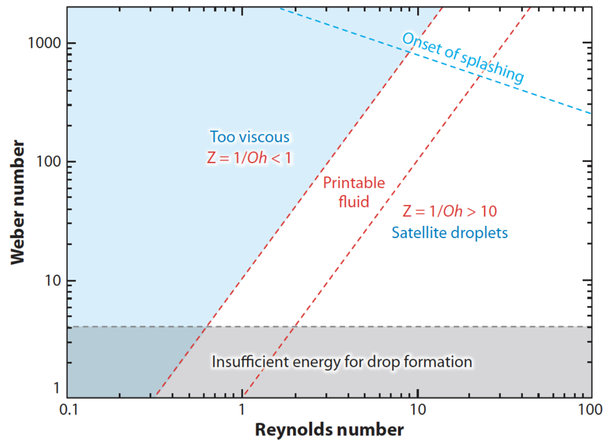


Figure 4

Equations 2–4, together with the range of $Z = 1/Oh$ that allows stable printing, can be plotted in a coordinate system defined by the Reynolds and Weber numbers to illustrate the regime of fluid properties where DOD inkjet printing is possible.

fluid dynamics, fluid mechanics and hydrodynamics

viscosity, drop formation, drop fall, drop impact, …

drying

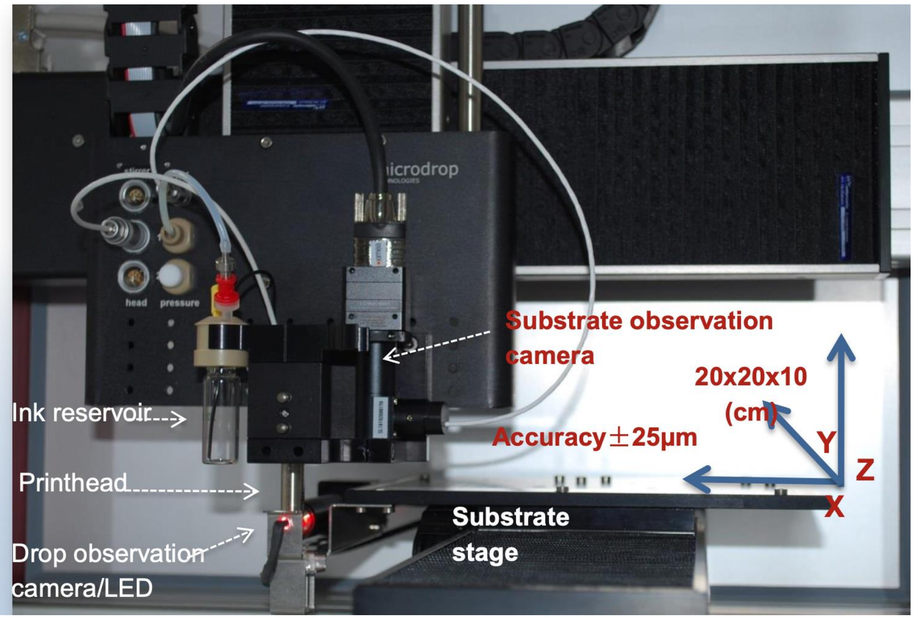
Piezo-actuated Inkjet

- ✓ Well defined pl droplet generation
- ✓ Small scale

Microdrop Technologies

Autodrop Compact

- ✓ Good control and observation (quantification) option
- ✓ Flexible design
  - space for modifications
  - Z-axis
- ✓ Two single nozzle printheads
- ✓ Applicable to low viscosity fluids



Derby B. Inkjet Printing of Functional and Structural Materials: Fluid Property Requirements, Feature Stability, and Resolution. Annu Rev Mater Res 2010;40:395–414. [Picture: Presentation from Zakharyuta, Sieger, Grube (Böhringer Ingelheim), 3D Medical Conference, Maastricht 2018]. Weber-Zahl: Zweiphasenströmungen, Verhältnis von Trägheitskraft zur stabilisierenden Oberflächenkraft; Reynolds-Zahl: Strömungslehre, Verhältnis von Trägheits- zu Zähigkeitskräften; Ohnesorge-Zahl: Einfluss der Zähigkeit auf die Deformation von Tropfen und Blasen.

… and Research

- Research cooperation
  - hospital pharmacy
    - international, national
- Academia
  - school of pharmacy
  - school of medicine
  - others
- Network, network, network!!!

How will the ideal 2D/3D-printer work?

will print ink, powder or other starting materials within a given set of specifications

➜ pH, compatible solvents, concentration/density, viscosity, temperature … …

will document all quality parameters (in-process)

➜ size of droplets, form of droplets, temperature, weight …

will be operated with parameters

➜ drops per mm^2, size of film, print design, weight, form …

Therefore development and production of „ink“/orodispersible films and other printing-starting-basis is possible for hospital pharmacists and not to be bought from printer vendors ➜ flexibility and speed

➜ compare to Ora-products (basis for extemporaneous production of oral liquids)

Conclusion

Drug development in hospital pharmacy is a prerequisite but also a must

Hospital pharmacy is responsible for the production of extemporaneous produced medicines and therefore has to have full control of the manufacturing process

We need a printer for „inks/filaments/semi-solids/powders/…“ which we can develop and produce by ourselves in the hospital pharmacy

University hospital pharmacies have an active role in patient focussed R&D

→ individualized/personalized drug development and production

Vielen Dank!

Fragen?