

# PRINTING PERSONALIZED CORTISOL FOR PATIENTS WITH ADRENAL INSUFFICIENCY.

From pharmaceutical development to clinical assessment.

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Pharmacist | PhD candidate



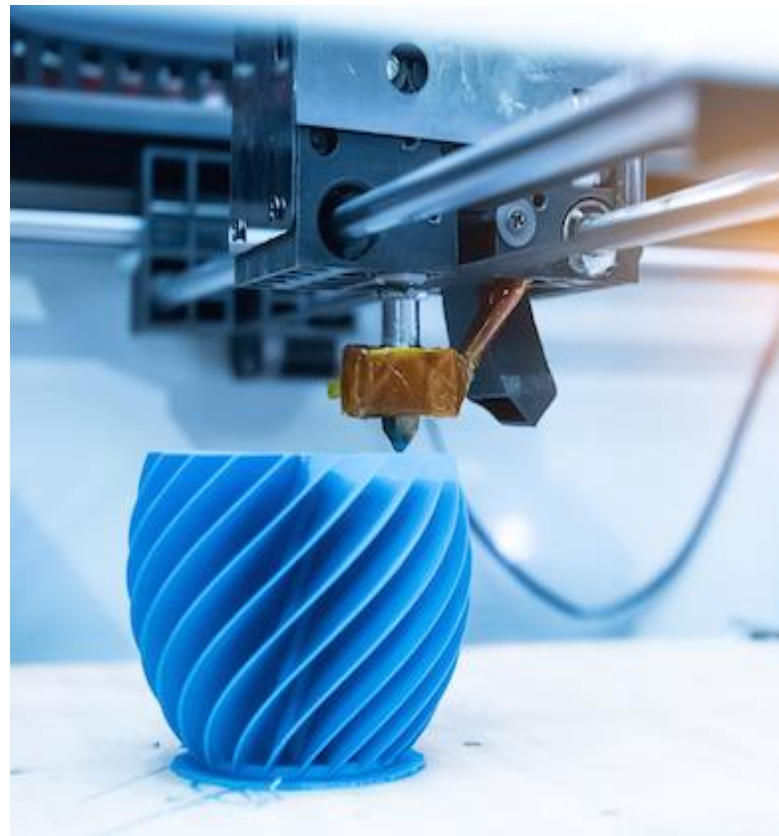
30-03-2022, Veldhoven

Erasmus MC  
University Medical Center Rotterdam

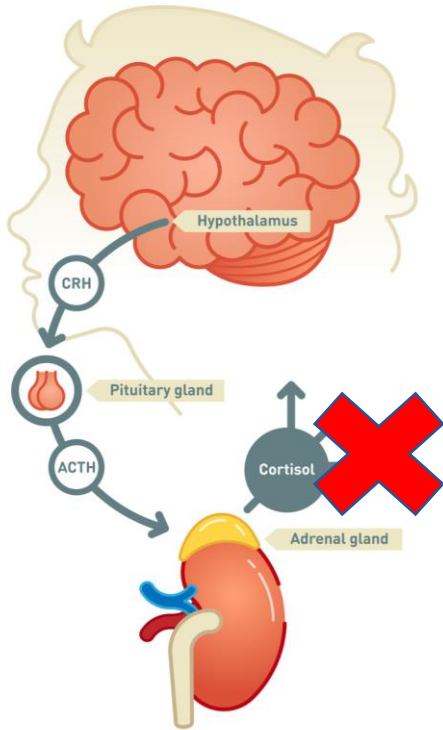


# Contents

1. Unmet medical need  
Adrenal insufficiency
2. Pharmaceutical development  
Fused deposition modeling (FDM)
3. Clinical trial  
Feasibility study



# Adrenal insufficiency



## Etiology

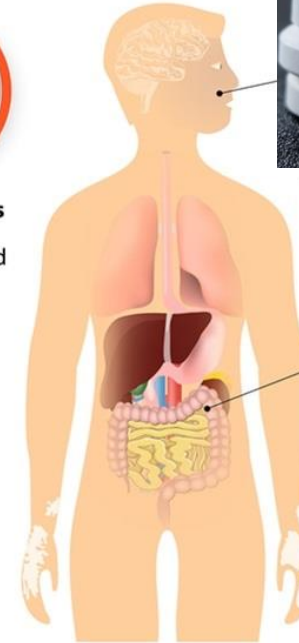
- Autoimmune destruction
- Infection
- Haemorrhage
- Drug-induced
- Genetic
- Etc...

## Addison's disease



**Adrenal glands**  
not produce  
sufficient steroid  
hormones

**Adrenal crisis:**  
- fever;  
- syncope;  
- convulsions;  
- hypoglycemia;  
- hyponatremia;  
- severe vomiting  
and diarrhea.



Low blood pressure  
Weakness  
Weight loss

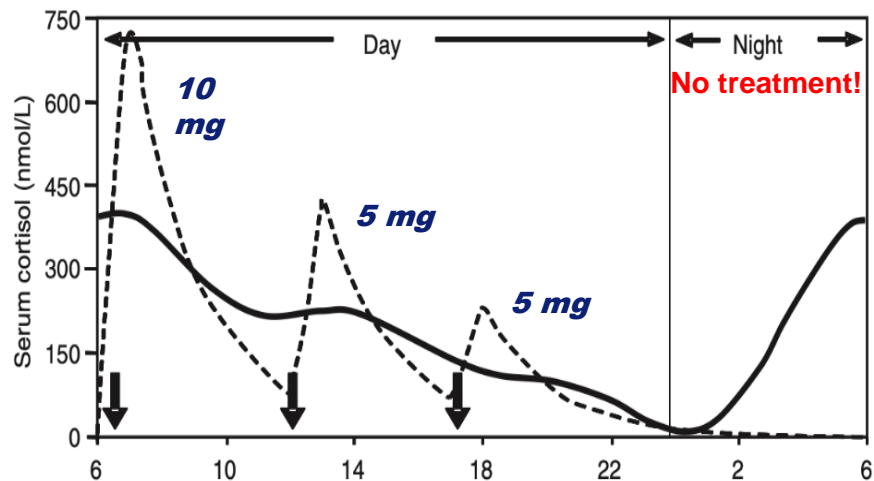
**Gastrointestinal**  
Nausea  
Diarrhea  
Vomiting  
Constipation  
Abdominal pain

**Skin**  
Vitiligo

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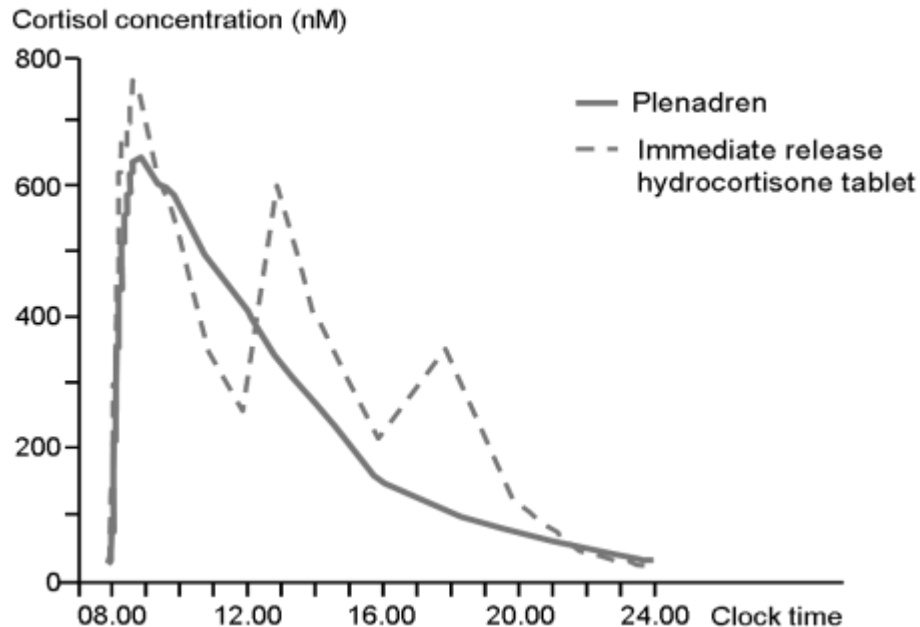
# Standard of care

- **Goal:** mimic physiological Cortisol
- **Over-replacement:** weigh gain, diabetes, osteoporosis
- **Under-replacement:** cardiovascular, mental, abdominal effects.



# Plenadren®

- Fixed dose (5 mg and 20 mg)
- No night-time cortisol
- Not standard of care
  - Costs?
  - Evidence?
  - Experience?
  - Stable patient?

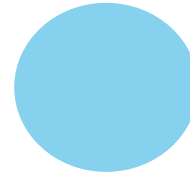


# Tailor made cortisol

- **Print tailored made formulation**
  - Dose/size
- **Night time cortisol**
  - Not waking up ill anymore
- **Therapy adherence**
  - Twice daily

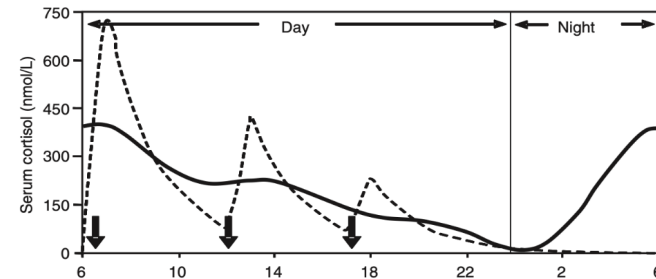
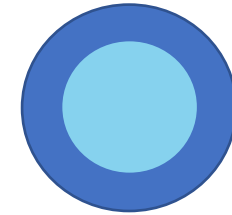
**Day time**

Sustained release



**Night time**

Delayed release



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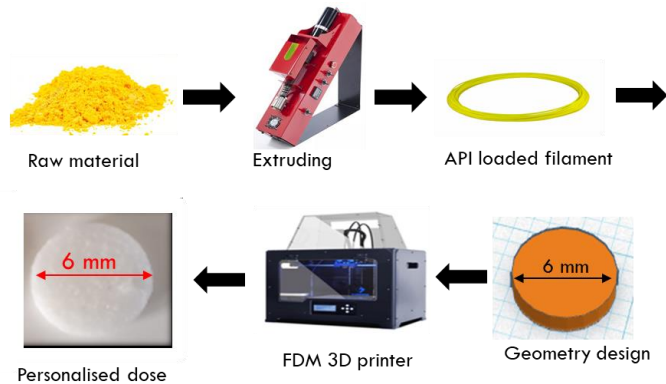


# Preformulation: sustained release (1)

## 1. Polymer selection

Formulation	HC	Mgs	PEG	KVA	HPC	EC
1	20	1	5	10	44	20
2	30	1	5	15	34	15

## 2. Manufacturing proces

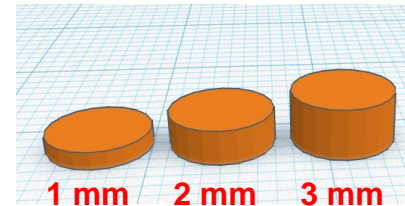


## 3. Temperature settings

Extrusion Ti	Extrusion Tf	Printing T	Platform T
110°C	170°C	200°C	50°C

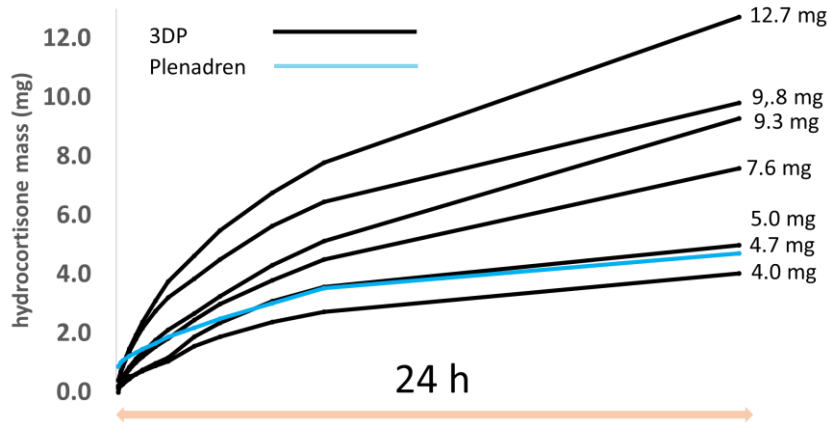
## 4. Final product

- Three designs



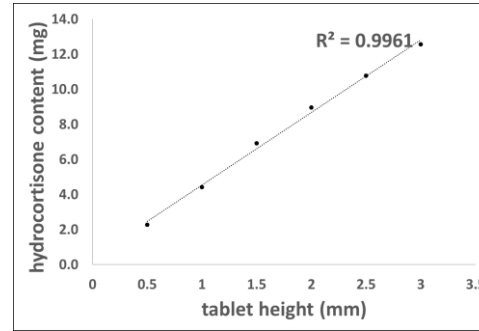
# Preformulation studies (2)

## 1. Dissolution



- Drug release > 80% in 24 h (Ph.Eur.)

## 3. Dose-height correlation



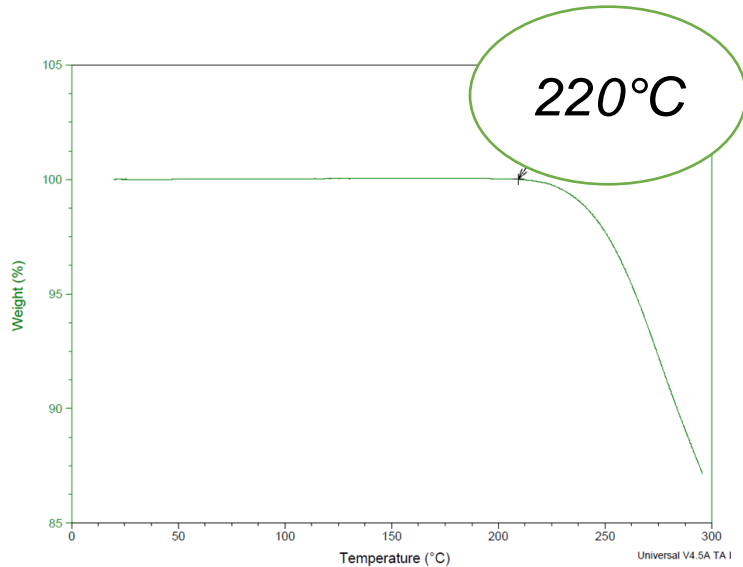
## 4. Formulation enhancement

Print temperature (°C)	Extrusion temperature (°C)	Average content tablet (%)
200	170	70,9



# Preformulation studies (3)

## 1. Identification of Tdeg



## 2. Optimum processing T

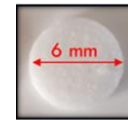
Print temperature (°C)	Extrusion temperature (°C)	Average content tablet (%)
200	170	70,9
190	170	76,5
180	170	85,9
170	170	89,7
160	160	86,8
150	150	91,7

## 3. Final product

200°C



150°C



# Towards final product..

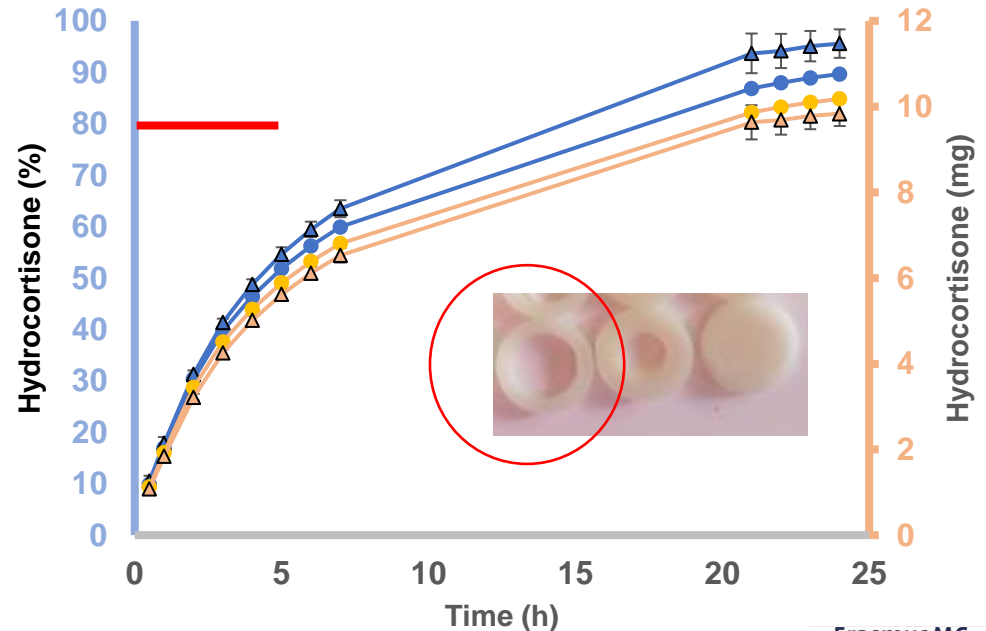
## 1. Formulation

Formulation	HC	Mgs	PEO	EuRL	HPC
	15	1	35	25	24

## 2. Temperature settings

Extrusion	Extrusion	Printing	Platform
110°C	150°C	150°C	50°C

## 3. Dissolution



# Towards final product..

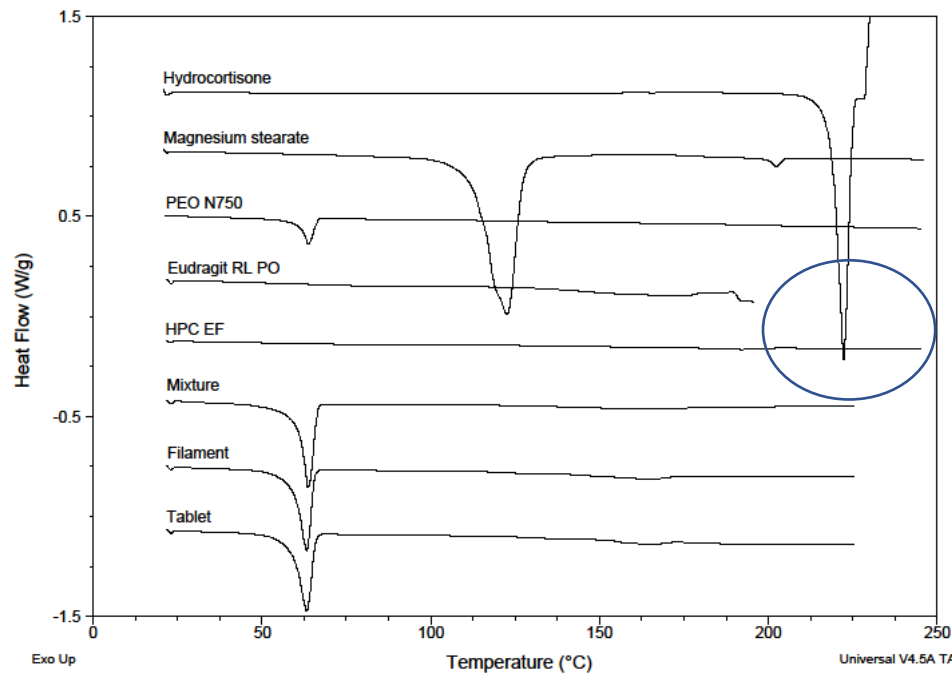
## 1. Printing resolution

Resolution	Average content (%)	SD
Low	93.6	0.08
Standard	93.1	0.59
High	90.5	1.99
Hyper	89.9	0.19

## 2. Friability

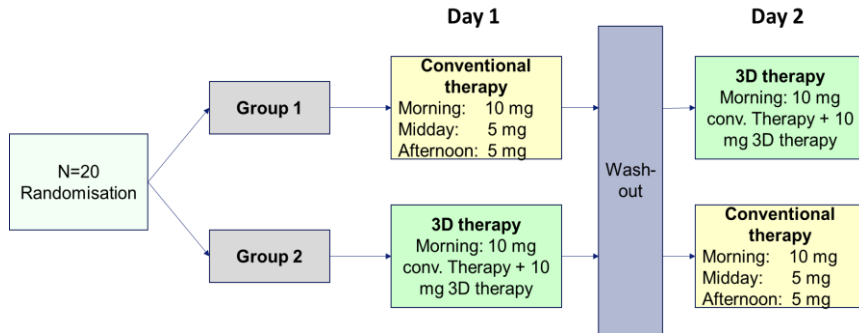
Ph.Eur	3D hydrocort
< 0.1%	0.06%

## 3. Differential scanning calorimetry

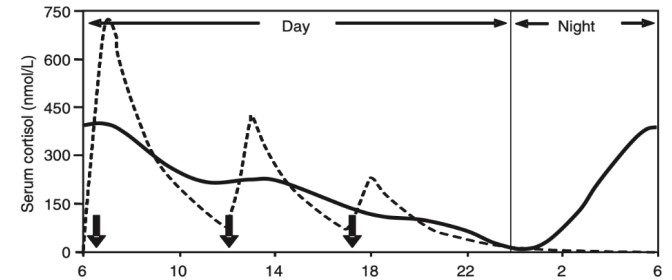


# 10 mg 3D SR hydrocortisone

- Feasibility study:
  - Adequate cortisol plasma concentration?



- Samples: blood, blood pressure
- Primary endpoint: AUC



# Future prospects

## Pharmaceutical

- Stability study
- Production sustained release
- Development delayed release

## Clinical studies

1. Clinical study delayed release hydrocortisone
2. RCT with combined 3D SR and DR vs. Standard of care



# Erasmus MC 3D team

Dr. E.J. Ruijgrok

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P.W.C. Meulenhoff

Dr. E.B. Wilms

E. Muller

M. Petremann

K. De Jager

# Erasmus MC 3D projects

1. Hydrocortisone sustained release
2. Hydrocortisone delayed release
3. **Flecainide** for children using semi-solid extrusion
4. **Liothyronine (T3) sustained release** for hypothyroidism